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Bisphosphonates and other bone agents for breast cancer (Review)

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TABLE OF CONTENTS

[Intervention Review]

Bisphosphonates and other bone agents for breast cancer

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ABSTRACT

Background

Bone is the most common site of metastatic disease associated with breast cancer (BC). Bisphosphonates inhibit osteoclast-mediated bone resorption, and novel targeted therapies such as denosumab inhibit other key bone metabolism pathways. We have studied these agents in both early breast cancer and advanced breast cancer settings. This is an update of the review originally published in 2002 and subsequently updated in 2005 and 2012.

Objectives

To assess the effects of bisphosphonates and other bone agents in addition to anti-cancer treatment: (i) in women with early breast cancer (EBC); (ii) in women with advanced breast cancer without bone metastases (ABC); and (iii) in women with metastatic breast cancer and bone metastases (BCBM).

Search methods

In this review update, we searched Cochrane Breast Cancer's Specialised Register, CENTRAL, MEDLINE, Embase, the World Health Organization's International Clinical Trials Registry Platform (WHO ICTRP) and ClinicalTrials.gov on 19 September 2016.

Selection criteria

We included randomised controlled trials (RCTs) comparing: (a) one treatment with a bisphosphonate/bone-acting agent with the same treatment without a bisphosphonate/bone-acting agent; (b) treatment with one bisphosphonate versus treatment with a different bisphosphonate; (c) treatment with a bisphosphonate versus another bone-acting agent of a different mechanism of action (e.g. denosumab); and (d) immediate treatment with a bisphosphonate/bone-acting agent versus delayed treatment of the same bisphosphonate/bone-acting agent.

Data collection and analysis

Two review authors independently extracted data, and assessed risk of bias and quality of the evidence. The primary outcome measure was bone metastases for EBC and ABC, and a skeletal-related event (SRE) for BCBM. We derived risk ratios (RRs) for dichotomous outcomes and the meta-analyses used random-effects models. Secondary outcomes included overall survival and disease-free survival for EBC; we

derived hazard ratios (HRs) for these time-to-event outcomes where possible. We collected toxicity and quality-of-life information. GRADE was used to assess the quality of evidence for the most important outcomes in each treatment setting.

Main results

We included 44 RCTs involving 37,302 women.

In women with EBC, bisphosphonates were associated with a reduced risk of bone metastases compared to placebo/no bisphosphonate (RR 0.86, 95% confidence interval (CI) 0.75 to 0.99; P = 0.03, 11 studies; 15,005 women; moderate-quality evidence with no significant heterogeneity). Bisphosphonates provided an overall survival benefit with time-to-event data (HR 0.91, 95% CI 0.83 to 0.99; P = 0.04; 9 studies; 13,949 women; high-quality evidence with evidence of heterogeneity). Subgroup analysis by menopausal status showed a survival benefit from bisphosphonates in postmenopausal women (HR 0.77, 95% CI 0.66 to 0.90; P = 0.001; 4 studies; 6048 women; high-quality evidence with no evidence of heterogeneity) but no survival benefit for premenopausal women (HR 1.03, 95% CI 0.86 to 1.22; P = 0.78; 2 studies; 3501 women; high-quality evidence with no heterogeneity). There was evidence of no effect of bisphosphonates on disease-free survival (HR 0.94, 95% 0.87 to 1.02; P = 0.13; 7 studies; 12,578 women; high-quality evidence with significant heterogeneity present) however subgroup analyses showed a disease-free survival benefit from bisphosphonates in postmenopausal women only (HR 0.82, 95% CI 0.74 to 0.91; P < 0.001; 7 studies; 8314 women; high-quality evidence with no heterogeneity). Bisphosphonates did not significantly reduce the incidence of fractures when compared to placebo/no bisphosphonates (RR 0.77, 95% CI 0.54 to 1.08, P = 0.13, 6 studies, 7602 women; moderate-quality evidence due to wide confidence intervals). We await mature overall survival and disease-free survival results for denosumab trials.

In women with ABC without clinically evident bone metastases, there was no evidence of an effect of bisphosphonates on bone metastases (RR 0.96, 95% CI 0.65 to 1.43; P = 0.86; 3 studies; 330 women; moderate-quality evidence with no heterogeneity) or overall survival (RR 0.89, 95% CI 0.73 to 1.09; P = 0.28; 3 studies; 330 women; high-quality evidence with no heterogeneity) compared to placebo/no bisphosphonates however the confidence intervals were wide. One study reported a trend towards an extended period of time without a SRE with bisphosphonate compared to placebo (low-quality evidence). One study reported quality of life and there was no apparent difference in scores between bisphosphonate and placebo (moderate-quality evidence).

In women with BCBM, bisphosphonates reduced the SRE risk by 14% (RR 0.86, 95% CI 0.78 to 0.95; P = 0.003; 9 studies; 2810 women; high-quality evidence with evidence of heterogeneity) compared with placebo/no bisphosphonates. This benefit persisted when administering either intravenous or oral bisphosphonates versus placebo. Bisphosphonates delayed the median time to a SRE with a median ratio of 1.43 (95% CI 1.29 to 1.58; P < 0.00001; 9 studies; 2891 women; high-quality evidence with no heterogeneity) and reduced bone pain (in 6 out of 11 studies; moderate-quality evidence) compared to placebo/no bisphosphonate. Treatment with bisphosphonates did not appear to affect overall survival (RR 1.01, 95% CI 0.91 to 1.11; P = 0.85; 7 studies; 1935 women; moderate-quality evidence with significant heterogeneity). Quality-of-life scores were slightly better with bisphosphonates than placebo at comparable time points (in three out of five studies; moderate-quality evidence) however scores decreased during the course of the studies. Denosumab reduced the risk of developing a SRE compared with bisphosphonates by 22% (RR 0.78, 0.72 to 0.85; P < 0.001; 3 studies, 2345 women). One study reported data on overall survival and observed no difference in survival between denosumab and bisphosphonate.

Reported toxicities across all settings were generally mild. Osteonecrosis of the jaw was rare, occurring less than 0.5% in the adjuvant setting (high-quality evidence).

Authors' conclusions

For women with EBC, bisphosphonates reduce the risk of bone metastases and provide an overall survival benefit compared to placebo or no bisphosphonates. There is preliminary evidence suggestive that bisphosphonates provide an overall survival and disease-free survival benefit in postmenopausal women only when compared to placebo or no bisphosphonate. This was not a planned subgroup for these early trials, and we await the completion of new large clinical trials assessing benefit for postmenopausal women. For women with BCBM, bisphosphonates reduce the risk of developing SREs, delay the median time to an SRE, and appear to reduce bone pain compared to placebo or no bisphosphonate.

PLAIN LANGUAGE SUMMARY

Bisphosphonates and denosumab for breast cancer

What is the issue?

Breast cancer may spread and recur in the bones. This may cause fractures, pain and high calcium in the bloodstream (known as complications).

Medicines for osteoporosis may prevent these complications and may help cure cancer by reducing cancer growth in the bone. These medicines are called 'bisphosphonates'. A newer type is called ‘denosumab’. Bisphosphonates or denosumab are given in addition to other cancer treatment medications. These may be given along with chemotherapy, endocrine therapy, or radiotherapy.

Study questions

The goal of bisphosphonates and denosumab differs based on the women's breast cancer status.

We asked three main questions:

1. For **women with early breast cancer (EBC)**, can bisphosphonates or denosumab reduce the risk of the cancer spreading to the bone? Will adding this medicine to anticancer treatments allow women to live longer (improve survival)?

2. For **women with advanced breast cancer which does not appear to involve the bone (ABC)**, can bisphosphonates reduce the risk of the cancer spreading to the bone and improve survival? Will bisphosphonates reduce complications and improve quality of life?

3. For **women with metastatic breast cancer that has spread to the bone (BCBM),** can bisphosphonates or denosumab reduce the risk of complication, and improve quality of life and survival?

Study Results

We found 44 studies involving 37,302 participants. We included studies published by September 2016.

Study results for women with early breast cancer (EBC)

For women with EBC, we included 17 studies with 26,129 participants. The women's health was monitored for at least 12 months from the start of the study. Some studies monitored women for 10 years.

The studies tested different types of bisphosphonate drugs and denosumab, and different doses of these drugs. Some studies compared the drugs to no treatment. Some studies used oral medications. Other studies gave the medicine as an injection into a vein or under the skin.

Bisphosphonates probably lowered the risk of cancer spreading to the bone.

Bisphosphonates were found to improve survival, but the benefit in the whole group of women was small. Postmenopausal women had a benefit from bisphosphonates with improved survival and reduced risk of cancer returning. Premenopausal women did not have improved survival or reduced risk of the cancer returning. New studies that test bisphosphonates by the women's menopausal status are awaited.

We await the reporting of data on survival and other important outcomes from denosumab trials.

Study results for women with advanced breast cancer (ABC)

For women with ABC that had not spread to the bone, we included three studies enrolling 330 participants. All three studies compared oral bisphosphonates to no treatment.

Bisphosphonates did not reduce the risk of cancer spreading to the bone or improve survival. Very little information was available on complications and quality of life from only one study.

Study results for women with metastatic breast cancer that has spread to the bone (BCBM)

For women with BCBM, we included 24 studies enrolling 10,853 participants. Their health was monitored for at least 12 months. Some women were followed for 24 months. Most studies compared bisphosphonates to receiving no medication.

Bisphosphonates reduced complications (fractures and bone pain). Bisphosphonates did not appear to increase the length of time women survived. Quality of life scores were slightly better for women receiving bisphosphonates compared to similar women having no bisphosphonates.

Denosumab reduced the risk of complications compared to bisphosphonates in the three studies that collected these data. There was no benefit in survival from denosumab in the one study that collected data.

Side effects for women with all types of breast cancer

Side effects were uncommon and mild. There was a rare risk of damage to the jaw bone ("osteonecrosis of the jaw").

Quality of the evidence

Overall, most of the evidence was moderate to high-quality. This means that we are fairly confident in the findings.

Summary of findings for the main comparison. Bisphosphonates compared to placebo/observation for women with early breast cancer

Bisphosphonates compared to placebo/observation for women with early breast cancer

Patient or population: women with early breast cancer
Setting: clinic and at home
Intervention: intravenous bisphosphonates (zoledronate 4 mg every 3 weeks) or oral bisphosphonates (clodronate 1600 mg/day or ibandronate 50 mg/day or pamidronate 300 mg/day)
Comparison: placebo/observation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo/observation	Risk with bisphosphonates				
Bone metastases Follow-up: range 1 year to 10 years	Study population		RR 0.86 (0.75 to 0.99)	15,005 (11 RCTs)	⊕⊕⊕⊖ Moderate[a]	Additional analysis of iv zoledronate or oral clodronate showed a treatment benefit when compared to placebo/control
	90 per 1000	77 per 1000 (67 to 89)				
Overall survival Follow-up: range 3 years to 10 years	3-year risk of death[b]		HR 0.91 (0.83 to 0.99)	13,949 (9 RCTs)	⊕⊕⊕⊕ High	
	80 per 1000	73 per 1000 (67 to 79)				
Overall survival postmenopausal women Follow-up: range 7 years to 7.5 years	50 per 1000[c]	39 per 1000 (33 to 45)	HR 0.77 (0.66 to 0.90)	6048 (4 RCTs)	⊕⊕⊕⊕ High	A sensitivity analysis removing ZO-FAST 2013 (due to the control arm being delayed bisphosphonate) showed equivalent efficacy (HR 0.78, 95% CI 0.66 to 0.92, 3 studies, 4984 women)
Overall survival: pre- or perimenopausal women Follow-up: range 5 years to 8 years	50 per 1000[c]	51 per 1000 (43 to 60)	HR 1.03 (0.86 to 1.22)	3501 (2 RCTs)	⊕⊕⊕⊕ High	
Disease-free progression follow-up: range 3 years to 10 years	3-year risk of recurrence[d]		HR 0.94 (0.87 to 1.02)	12578 (7 RCTs)	⊕⊕⊕⊕ High	
	120 per 1000	113 per 1000 (105 to 122)				

Disease-free progression: postmenopausal women Follow-up: range 3 years to 7.8 years	110 per 1000[e]	91 per 1000 (83 to 101)	HR 0.82 (0.74 to 0.91)	8314 (7 RCTs)	⊕⊕⊕⊕ High	A sensitivity analysis removing Z-FAST 2012 and ZO-FAST 2013 (due to the control arm being delayed bisphosphonate), showed equivalent efficacy (HR 0.83, 95% CI 0.74 to 0.93; 5 studies; 6650 women)
Disease-free progression: pre- or peri-menopausal women Follow-up: range 3 years to 7.5 years	110 per 1000[e]	111 per 1000 (100 to 124)	HR 1.01 (0.90 to 1.13)	5493 (4 RCTs)	⊕⊕⊕⊕ High	
Fracture incidence Follow-up: range 5 years to 7.8 years	Study population 58 per 1000	44 per 1000 (31 to 62)	RR 0.77 (0.54 to 1.08)	7602 (6 RCTs)	⊕⊕⊕⊖ Moderate[f]	Three studies used iv bisphosphonate (zoledronate) and three studies used oral bisphosphonate (clodronate or pamidronate) compared to placebo
Osteonecrosis of the jaw (ONJ) Follow-up: range 1 year to 7.5 years	Bisphosphonates: approximately 35 events of ONJ were recorded in 7047 women Placebo/open: no events of ONJ were recorded in 6195 women		-	13,242 (9 RCTs)	⊕⊕⊕⊕ High[g]	Six studies used iv bisphosphonates (zoledronate) and three studies used oral bisphosphonates (ibandronate or clodronate). Most ONJ events came from 2 studies using iv zoledronate (AZURE 2014 & NATAN 2016)
Infusion-related side effects	Seven studies reported 1 or 2 infusion-related side-effects (e.g. fever, fatigue, nausea or influenza-type symptoms). Intravenous bisphosphonate (zoledronate) appeared to slightly increase the incidence of fever (in 3 out of 5 studies), fatigue (in 2 out of 3 studies) and nausea (in 2 out of 3 studies) compared to placebo. However the reporting of the grade toxicity was sometimes unspecified or on different scales.		-	(7 RCTs)	⊕⊕⊕⊖ Moderate[h,i]	Fever: 6070 women (5 studies), fatigue: 2599 women (3 studies), nausea: 3825 women (3 studies), influenza-type symptoms: 103 women (1 study)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **HR**: hazard ratio; **iv**: intravenous; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]Outcome assessors were either part of an independent adjudication committee or blinded to the treatment allocation in 5 out of 11 studies. We downgraded for risk of bias by 1 point because this outcome measure may be influenced by a lack of blinding in the other 6 studies.
[b]The baseline risk in the control group was based on the average of the 3-year estimates from nine studies.
[c]The baseline risk in the control group for pre- and postmenopausal women were averages of the 3-year estimates from the contributing studies.
[d]The baseline risk in the control group was based on the average of the 3-year estimates from seven studies.
[e]The baseline risk in the control group was based on the average of 3-year estimates from the contributing studies.
[f]The confidence intervals are wide and we downgraded by 1 point for imprecision.
[g]There was a very low event rate so we decided not to downgrade for imprecision.
[h]Differences in reporting of grades of toxicity with some reporting grade 3/4 toxicity and other toxicity scales unspecified. Given this variability, we did not meta-analyse the data. However the results appeared to be fairly consistent and we did not view this as a serious concern (therefore did not downgrade the quality of evidence).
[i]Three out of the seven studies were open-label studies and lack of blinding may impact on the patient-reported subjective outcomes. We downgraded for risk of bias by 1 point.

Summary of findings 2. Bisphosphonates compared to placebo/observation for women with advanced breast cancer without bone metastases

Bisphosphonates compared to placebo/observation for women with advanced breast cancer without bone metastases

Patient or population: women with advanced breast cancer without bone metastases
Settings: clinic and at home
Intervention: oral bisphosphonates (clodronate 1600 mg/day or pamidronate 300 mg/day)
Comparison: placebo or observation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo/observation	Risk with bisphosphonates				
Bone metastases Follow-up: range 16 months to 84 months	Study population		RR 0.96 (0.65 to 1.43)	330 (3 RCTs)	⊕⊕⊕⊖ Moderate[a]	
	235 per 1000	225 per 1000 (152 to 335)				
Median time to a skeletal-related event (SRE) Follow-up: median 84 months	We did not observe any statistically significant benefit using the bisphosphonate, oral clodronate. The median time to an SRE with clodronate was 28.4 months compared to 13.4 months with placebo (P = 0.42)		-	73 (1 RCT)	⊕⊕⊖⊖ Low[b,c]	
Overall survival	Risk of death		RR 0.89 (0.73 to 1.09)	330 (3 RCTs)	⊕⊕⊕⊕ High[d]	

Follow-up: range 16 months to 84 months	556 per 1000	494 per 1000 (406 to 606)			
Quality of life assessed with 4-point scale Follow-up: range 16 months to 20 months	Similar quality-of-life scores with bisphosphonates (pamidronate) or no bisphosphonates	-	124 (1 RCT)	⊕⊕⊕⊝ Moderate[e]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]Downgraded for imprecision because the confidence intervals included no effect and appreciable benefit and harm.
[b]12 out of the 73 participants did not receive treatment for at least 2 months and were not followed-up. We judged this study to be at high risk of bias for incomplete outcome data and we downgraded risk of bias by 1 point.
[c]Only one study that had a small sample size reported this outcome and the estimates of effect appear to have wide confidence intervals. We downgraded for imprecision by 1 point.
[d]We did not downgrade for imprecision as the confidence intervals were considered sufficiently narrow enough for an all-encompassing outcome such as overall survival.
[e]Quality-of-life measures were patient-reported; the study was an open-label trial and deemed to be at high risk of bias for not blinding participants to their treatment allocation. We downgraded risk of bias by 1 point. We did not downgrade the quality of evidence on other domains due to only one study contributing to this outcome (as permitted by GRADE guidance).

Summary of findings 3. Bisphosphonates compared to placebo/observation for women with metastatic breast cancer and bone metastases

Bisphosphonates compared to placebo/observation for women with metastatic breast cancer with bone metastases

Patient or population: women with metastatic breast cancer with bone metastases
Setting: clinic and at home
Intervention: intravenous bisphosphonates (pamidronate (45 to 90 mg/day) or ibandronate (6 mg) or zoledronate (4 mg)) or oral bisphosphonates (clodronate (1600 mg/day) or ibandronate (50 mg) or pamidronate (300 mg))
Comparison: placebo or observation

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments

	Risk with placebo/observation	Risk with bisphosphonates				
Skeletal-related event (SRE) Follow-up: range 12 months to 24 months	Study population		RR 0.86 (0.78 to 0.95)	2810 (9 RCTs)	⊕⊕⊕⊕ High[a]	Additional analyses of iv or oral bisphosphonates vs placebo showed equivalent efficacy
	640 per 1000	550 per 1000 (499 to 608)				
Median time to a skeletal-related event Follow-up: range 12 months to 24 months	Bisphosphonates significantly delayed the median time to an SRE compared to placebo/observation (in 11 out of 12 studies that reported results but not sufficiently to be included in a meta-analysis). The median time to an SRE in the bisphosphonates group ranged from 8.7 to 20.8 months while the placebo group ranged from 4.9 to 14.9 months		Median ratio 1.43 (1.29 to 1.58)	2891 (9 RCTs)	⊕⊕⊕⊕ High	Significant benefits were observed using iv bisphosphonates (7 studies) and oral bisphosphonates (4 studies) vs placebo
Overall survival Follow-up: range 12 months to 24 months	Risk of death		RR 1.01 (0.91 to 1.11)	1935 (7 RCTs)	⊕⊕⊕⊖ Moderate[b]	Analyses of iv or oral bisphosphonates vs placebo showed similar results
	575 per 1000	581 per 1000 (523 to 638)				
Bone pain assessed with: Brief Pain Inventory, visual analog/pain scales and other validated or unvalidated scales Follow-up: range 12 months to 24 months	Bisphosphonates significantly reduced bone pain compared to placebo (in 6 out of 11 studies). Bone pain was reduced with bisphosphonates in another 3 studies but the effect was not statistically significant or P value not reported		-	3297 (11 RCTs)	⊕⊕⊕⊖ Moderate[c,d]	Bone pain was assessed using a wide range of scales across studies and only 6 studies used a validated scale (e.g. Brief Pain Inventory). Significant benefits observed using iv bisphosphonates (3 studies) and oral bisphosphonates (3 studies) when compared to placebo
Quality of life assessed with: EORTC Quality of Life Scale - Core 30 questionnaire (QLQ-C30), trial-specific questionnaires, Spitzer quality of life, FACT-G Follow-up: range 12 months to 24 months	Quality-of-life scores were better with bisphosphonates than placebo at comparable timepoints (in 3 out of 5 studies). Quality-of-life scores decreased during the studies as disease progressed		-	1888 (5 RCTs)	⊕⊕⊕⊖ Moderate[e,f]	The studies used validated questionnaires (in one study a trial-specific but validated one) and unvalidated scales

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: Confidence interval; **iv**: intravenous; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

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[a]We did not downgrade for heterogeneity. This is because when two studies that used relatively low doses of pamidronate (45 mg or 60 mg) and contributed largely to the heterogeneity were removed from the meta-analysis, the beneficial effect of bisphosphonates compared to placebo persisted.

[b]Not all confidence intervals overlapped and the point estimate varied widely across studies. We downgraded inconsistency by 1 point.

[c]Measures were self-reported; 8 out of the 17 studies that reported bone pain scores were at high risk of bias for non-blinding of participants to their treatment allocation. We downgraded risk of bias by 1 point.

[d]Given that bone pain was assessed on various scales, we did not meta-analyse the data. However the results appeared to be fairly consistent and we did not view this as a serious concern (therefore did not downgrade the quality of evidence).

[e]Measures were patient-reported; 3 out of the 8 studies that reported on quality of life were at high risk of bias for non-blinding participants to their treatment allocation. We downgraded risk of bias by 1 point.

[f]Given the variability in reporting quality-of-life results across studies, we were unable to meta-analyse the data. We did not judge inconsistency across the studies as a serious concern and therefore did not downgrade the quality of the evidence.

BACKGROUND

Description of the condition

Breast cancer is the most common cancer, and the most common cause of cancer death in women worldwide (WHO 2003; Ferlay 2015). Bone is the most common site of metastatic involvement, affecting more than half of women during the course of their disease (Scheid 1986). Although survival is better in women with advanced breast cancer (ABC) if their metastases are confined to bone (Coleman 1987), bone metastases cause significant morbidity due to pain, pathological fracture, hypercalcaemia and spinal cord compression, as well as contributing to mortality (Coleman 1985). Breast cancers with bone metastases (BCBM) are predominantly osteolytic (50%) or mixed osteolytic and osteoblastic (40%), with only a small proportion (about 10%) being osteoblastic alone (Harvey 1997).

The pathophysiology of bone metastases includes increased bone turnover, imbalance and uncoupling of the processes of resorption and remodelling (Kanis 1995). Osteoclasts are primarily responsible for the bone resorption of lytic metastases (Mundy 1997) and are involved in a complex osteolytic cycle that involves parathyroid hormone-related peptide (PTHrP), receptor activator of nuclear factor (NF)-κB ligand (RANK-L), osteoprotegerin (OPG), transforming growth factor beta (TGF-b) and many other transcription factors. Tumours secrete PTHrP that stimulates osteoblasts, which respond by secreting RANK-L and inhibiting OPG. The increased RANK-L/OPG gradient drives the activation of osteoclasts, which in turn produces TGF-b and other growth factors, all having a profound effect on tumour growth. In this way, tumour and osteoclasts are engaged in a self-perpetuating cycle, where tumour and osteoclasts provide fuel for each other (Kozlow 2005).

Description of the intervention

Before the era of bisphosphonates, the management of symptomatic bone disease depended on analgesics, radiotherapy, endocrine therapy and chemotherapy. Despite these frequently effective treatments, progressive skeletal destruction often leads to ongoing symptoms and deterioration of quality of life (Mundy 1991).

Bisphosphonates inhibit osteoclastic bone resorption (Rogers 1997). They are effective in conditions characterised by osteoclast-mediated bone resorption such as Paget's disease and osteoporosis (Russell 1999). In malignancy, they have become standard treatment for tumour-induced hypercalcaemia (Body 1998).

How the intervention might work

RCTs have shown that in multiple myeloma, breast cancer and prostate cancer, bisphosphonates reduce bone pain, improve quality of life, and reduce the number of and time to skeletal-related event (SREs) (Bloomfield 1998; Body 1998). In addition, pre-clinical work has suggested that bisphosphonates have an anti-tumour activity, acting through inhibiting cell migration and invasion, and inducing apoptosis in breast cancer cells (Hiraga 2004).

Why it is important to do this review

It is therefore of interest to examine the adjuvant role of bisphosphonates in women with early breast cancer (EBC). Aside from bisphosphonates, many novel agents that specifically target the vicious cycle of bone metastases are being developed. Whilst many are still in the early stages of drug development, RANK-ligand inhibitor denosumab has already completed phase III clinical trials in breast and prostate cancers (Fizazi 2011; Stopeck 2010). It is with great anticipation that we see where denosumab, with superior efficacy and good tolerability, fits in to clinical practice for women with BCBM.

The aim of this systematic review was to identify, describe and summarise high-quality evidence regarding the use of bisphosphonates and other bone agents in women with early, advanced and metastatic breast cancer. This review was first published in 2002 and was updated in 2005, 2007, 2012 and now in 2017.

OBJECTIVES

To assess the effects of bisphosphonates and other bone agents in addition to anti-cancer treatment: (i) in women with early breast cancer (EBC); (ii) in women with advanced breast cancer without bone metastases (ABC); and (iii) in women with metastatic breast cancer and bone metastases (BCBM).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Women with a history of breast cancer.

Types of interventions

RCTs in women with either EBC, ABC or BCBM:

1. one treatment with a bisphosphonate/bone-acting agent with the same treatment without a bisphosphonate/bone-acting agent (placebo/observation);
2. treatment with one bisphosphonate compared with treatment with a different bisphosphonate;
3. treatment with a bisphosphonate compared with another bone-acting agent of a different mechanism of action; and
4. immediate treatment with a bisphosphonate/bone-acting agent compared with delayed treatment of the same bisphosphonate/bone-acting agent.

We included studies with:

1. bisphosphonates administered orally or intravenously, in any dose and for any duration;
2. bone-acting agents (e.g. denosumab) administered in any dose and for any duration; and
3. placebo groups and studies with open control groups (no treatment)

Types of outcome measures

Primary outcomes

1. For women with EBC (defined by stage I-III breast cancer with no distant metastases, locally advanced or recurrent disease):
   a. bone metastases
2. For women with ABC (defined by locally ABC, recurrent breast cancer or metastatic breast cancer with no clinically evident bone metastases):
   a. bone metastases
3. For women with BCBM:
   a. the proportion of women on treatment experiencing a SRE compared to control, expressed as a risk ratio (RR). (For this systematic review, reducing the proportion of women with a SRE was synonymous with reducing the risk of developing a SRE and preventing a SRE).

Secondary outcomes

1. For women with EBC (defined by stage I-III breast cancer with no distant metastases, locally advanced or recurrent disease):
   a. visceral metastases;
   b. locoregional recurrence;
   c. recurrence (defined by locoregional recurrence and distant recurrence);
   d. overall survival (or death);
   e. disease-free survival;
   f. fracture incidence;
   g. quality of life; and
   h. adverse, drug-related events or toxicity.
2. For women with ABC (defined by locally ABC, recurrent breast cancer or metastatic breast cancer with no clinically evident bone metastases):
   a. SRE, expressed as a RR (treatment group versus control group);
   b. SRE rate (where reported)
   c. median time to a SRE, expressed as a median ratio (treatment group versus comparator group);
   d. overall survival;
   e. quality of life; and
   f. adverse, drug-related events or toxicity.
3. For women with BCBM:
   a. SRE, expressed as a RR (treatment group versus comparator group);
   b. SRE rate (where reported)
   c. median time to a SRE, expressed as a median ratio (treatment group versus comparator group);
   d. overall survival;
   e. bone pain
   f. quality of life; and
   g. adverse, drug-related events or toxicity.

We considered for evaluation studies including at least one of the following outcomes.

1. SREs (new bone metastases; pathological fractures; spinal cord compression; irradiation or surgery on bone; and bone pain).
2. recurrence; and
3. quality of life.

We did not include studies if they only reported death and none of the above SRE endpoints.

Search methods for identification of studies

Electronic searches

For this review update, we searched the following databases or registries on the 19 September 2016.

1. The Specialised Register maintained by Cochrane Breast Cancer. Details of the search strategies used by the group for the identification of studies and the procedure used to code references are outlined in the group's module in The Cochrane Library (www.mrw.interscience.wiley.com/cochrane/clabout/articles/BREASTCA/frame.html). The Specialised Register includes both published and unpublished (including ongoing) trials. Trials coded with the key or text words 'bisphosphonate/s' or 'diphosphonate/s' as well as each specific bisphosphonate (zoledronate, zoledronic acid, pamidronate, clodronate, ibandronate, etidronate, alendronate, risedronate, incadronate, olpadronate, neridronate) 'RANK ligand inhibitor', 'Denosumab', 'Prolia' and 'Xgeva' were combined with 'breast cancer', and we extracted and considered them for inclusion in the review.
2. Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 8) in the Cochrane Library (searched 19 September 2016). See Appendix 1
3. MEDLINE (via OvidSP) on 19 September 2016. See Appendix 2
4. Embase (via OvidSP) on 19 September 2016. See Appendix 3
5. The WHO International Clinical Trials Registry Platform (ICTRP) search portal (apps.who.int/trialsearch/Default.aspx) for all prospectively registered and ongoing trials. See Appendix 4.
6. ClinicalTrials.gov (clinicaltrials.gov/ct2/home). See Appendix 5.

We did not apply any restrictions based on language.

For details regarding the searches conducted in previous versions of this review, please refer to Pavlakis 2002, Pavlakis 2005 and Wong 2012.

Searching other resources

We searched databases of major international oncology conferences (i.e. the American Society of Clinical Oncology (ASCO) and San Antonio Breast Cancer Symposium (SABCS)) for relevant references using Embase.com.

We also evaluated systematic reviews published between 2007 and 2016 and searched their reference lists for any additional trials that may have been missed in the initial database search. We also contacted study sponsors and other bisphosphonates investigators to identify additional studies and results. We received permission from pharmaceutical companies to include these studies. These are found in the Characteristics of ongoing studies section.

Data collection and analysis

Selection of studies

For the original and updated review versions, two review authors (2016 update: BOC, AG) independently screened the abstracts and full-text articles (where available) against the eligibility criteria. Where necessary, we referred any disagreements to a third reviewer

for an additional independent evaluation however this was not required in the 2016 update. Final assessment was then determined by consensus with all authors.

Data extraction and management

The primary reference to each study was usually the final or updated published version of each paper, however for some studies, we extracted data from more than one publication. Each review author independently extracted data using data collection forms similar to the Characteristics of included studies (2016 update: BOC, MLW or AG). The data collected included methods, participants, interventions and other treatments, primary and secondary outcomes, statistical analysis, baseline characteristics and results. Where possible, we quoted the study authors' own words so that data extraction was as objective as possible. If there was disagreement between review authors on data extraction then a third review author (MLW or AG) independently extracted the data before we reached a consensus.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias (2016 update: BOC, MLW or AG). A third review author resolved any disagreements by consensus (AG). For recent review updates, we assessed the studies by using the Cochrane 'Risk of bias' tool as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We used the standard 'Risk of bias' tables by default to describe a detailed appraisal of the study with focus on the selection bias (random sequence generation, allocation concealment), measurement bias (blinding), attrition bias (incomplete outcome data analysis), selective outcome reporting and other identified sources of bias. We thoroughly searched each study for these risk of bias domains and extracted information for the purpose of a critical appraisal. We rated each domain as either 'low risk' or 'high risk' of bias. Where the primary references did not provide sufficient details, we resorted to secondary references, abstracts, presentations or protocols. Where there was still insufficient information despite attempts to clarify details, we rated the domain as having an 'unclear risk' of bias.

Measures of treatment effect

For the outcome measure of SREs, we have relied on the total number of SREs reported in each paper, in preference to adding together the numbers of each type of SRE. Unfortunately, the reporting of SREs, and in particular the rate of events over time, varied across the studies. Methodology reviews of multiple event reporting such as events per person per year, which assume constant event rates per participant in a given time, have been criticised as providing inaccurate methods for reporting SRE rates within bisphosphonate studies (Cook 2001). Consistent methods of multiple event analyses suitable for bisphosphonate studies were described but are yet to be consistently used in the more recent studies (Andersen 1982). Only a post-hoc re-analysis of the single zoledronate versus pamidronate study reported SRE rates calculated in this way (Andersen 1982; Rosen 2004).

Due to the differences in the way outcomes were reported, we have reported SRE data as number of events during the studied period and risk ratios (RRs), and as time to events. We have expressed the size of the difference between time-to-event distributions as the ratio of the median time to event in the experimental arm over the same outcome in the comparator arm. For a time to SRE, a value over 1.0 suggests superiority for the experimental arm and a value under 1.0 suggests superiority for the comparator arm. We have not formally combined these ratios of SRE rates. Unlike previous versions of this review, this update has presented the median time to a SRE for bisphosphonates versus control as a meta-analysis. We used the method proposed by Michiels 2005 by calculating the ratio of the medians and presenting these on a log scale using the general inverse variance method in Review Manager 5 (RevMan 5) (RevMan 2014).

For the endpoint of recurrence in EBC studies, the trial authors often reported recurrence together with death (recurrence-free survival) or partitioned into bone metastases, visceral metastases and locoregional recurrence. Since this endpoint needed to be integrated from different components to form an aggregate, for the purpose of this review we have clearly defined recurrence as locoregional plus distant metastases only, and have not included a new primary, contralateral or ipsilateral breast cancer. We have cross-checked the recurrent events by summing up the specified events where the numbers were provided by the trial authors. We have been cautious to include the first event per participant only, so that participants with more than one type of recurrence have not been counted twice. We derived a pooled RR with 95% confidence interval (CI). In addition, we have not presented this outcome as a hazard ratio (HR) due to many studies failing to report the outcome as such and the substantial variation in reporting results across studies.

For the outcome measures of disease-free survival and overall survival in early breast cancer studies, we derived the HR, as it is the most appropriate statistic. When possible, we extracted the HR and associated variances directly from the trial publication(s) or they were provided by the trial authors. If it was not reported, we obtained it indirectly employing the methods described by Tierney and colleagues using other available summary statistics (Tierney 2007). A HR less than 1.0 favoured the experimental arm. In addition to reporting these outcomes as time to event, we reported data as events and RRs for each study based on reporting preferences in the previous version of this review. In this review update, we have presented data as both time-to-event data and dichotomous outcomes for comparison.

For the outcome measures of bone pain and quality of life, the data reported by the trial authors were particularly varied, with some studies utilising nominal visual analogue scales and others using validated questionnaires such as the EORTC-QLQ-C30 or Brief Pain Inventory. We have restricted the description and synthesis to those studies from which we have extracted suitable data. We have only included, in the relevant tables, studies for which these outcomes were directly assessed. We have used a qualitative scale to summarise their judgment of whether the results indicated a significant difference, a trend or no difference in bone pain and quality of life between groups.

For toxicity, we have reported adverse events descriptively in Tables.

Unit of analysis issues

In the adjuvant setting, ABCSG-12 2011 was a two-by-two factorial trial that randomised women to either anastrozole or tamoxifen with or without zoledronate. For the purpose of this review, we included data for the zoledronate versus no-zoledronate

comparison. GAIN 2013 was also a two-by-two factorial trial that involved two comparisons: (1) 2:1 ibandronate versus observation and (2) 1:1 different dose-dense arms. We included the data relating to the ibandronate versus observation comparison in this review. Some participants that did not start the parallel chemotherapy and were excluded from the ibandronate (n = 19) and observation (n = 10) comparison. SWOG-S0307 2015 was a three-armed study comparing zoledronate, clodronate and ibandronate, and results were reported in two abstracts. Due to limited information in the abstract, we have presented results narratively where possible.

In the BCBM setting, six studies were three-armed trials (Body 2003; Diel 1999; Fizazi 2009; Rosen 2004; Tripathy 2004; von Au 2016). The three treatment regimens in Fizazi 2009 were eligible for two comparisons: (1) immediate versus delayed administration of a bone-acting agent (denosumab) and (2) other bone-acting agent (denosumab) versus bisphosphonate (intravenous zoledronate). For the denosumab-bisphosphonate comparison, the pharmaceutical company (Amgen) provided data to the review authors with new data integrated in the previous version of this review. In Body 2003, there were two experimental arms (intravenous ibandronate 6 mg and 2 mg, every 3 to 4 weeks) and one control (placebo) arm; only data from the 6 mg and placebo were used in the analysis. Similarly, in Tripathy 2004, only one of the experimental arms (oral ibandronate 50 mg a day rather than 20 mg a day) was compared against the control (placebo) arm and reported in this review. Diel 1999 included three experimental arms, intravenous clodronate, oral clodronate and intravenous pamidronate and reported data in abstract form only; we included data from Diel 1999 narratively in the review for all three arms where available. Rosen 2004 initially tested intravenous zoledronate 8 mg or intravenous zoledronate 4 mg as a 15-minute infusion against intravenous pamidronate 90 mg as a two-hour infusion, however the trial authors only reported efficacy data for the 4 mg zoledronate and intravenous pamidronate groups. von Au 2016 used intravenous clodronate (900 mg every 3 weeks) or oral clodronate (2400 mg per day) against intravenous pamidronate (60 mg every 3 weeks); we reported data from all three treatment arms where available.

Dealing with missing data

We contacted trial authors (Aft 2012; AZURE 2014; Fizazi 2009; GAIN 2013; Kristensen 2008; NATAN 2016) for additional information not in the published trial to permit meta-analysis.

Assessment of heterogeneity

We used the Chi^2 test and the I^2 statistic (Higgins 2003) to test for heterogeneity over all studies, as well as visual inspection of forest plots (Deeks 2011). For the Chi^2 test, a P value of 0.10 indicated evidence of heterogeneity. We used the I^2 statistic as a rough guide to assess heterogeneity: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% considerable heterogeneity. We evaluated the value of the I^2 statistic alongside the magnitude and direction of effects, and the P value for the Chi^2 test (Deeks 2011).

We used the random-effects model in this systematic review by default unless otherwise stated, as the studies we included (especially EBC studies) were heterogeneous in methodology, design, participant groups, disease stage and other treatment. A random-effects model assumed a different underlying effect of each study and took into account the weighted average of trials of smaller effect. With this model, the meta-analyses were more likely to represent the typical effect in the observed studies.

We considered and discussed heterogeneity in parts of the Effects of interventions and Discussion sections of the review.

Assessment of reporting biases

We assessed reporting bias using Cochrane's 'Risk of bias' tool (Higgins 2011). We used trials registers (WHO ICTRP and ClinicalTrials.gov) and published protocols (where available) to cross-check the reporting of outcomes in the trial publications.

We followed the recommendations for testing for funnel plot asymmetry as described in section 10.4.3.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2011). Funnel plot asymmetry may be due to reporting bias and we addressed this possibility in the Effects of interventions section of the review.

Data synthesis

For dichotomous outcomes (i.e. SREs, bone metastases, visceral metastases, locoregional recurrence, overall recurrence), we obtained a pooled RR using the random-effects model (Mantel-Haenszel analysis). For SRE data as time to events and rates, we did not formally combine the data due to variations in reporting but collated data in tables and synthesised them narratively.

For time-to-event outcomes (i.e. disease-free survival and overall survival), we obtained a pooled HR using the fixed-effect (inverse-variance method) analysis. For the median time to a SRE, we obtained a pooled median ratio (with data entered on a log scale) using the fixed-effect (inverse-variance method) analysis.

We have narratively described and presented bone pain, quality of life and adverse events in tables.

We performed all analyses using RevMan 5 software (RevMan 2014) in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011a).

'Summary of findings' tables:

We used the GRADE approach to assess the quality of evidence for the following main outcomes in each setting.

EBC

1. Bone metastases
2. Overall survival
3. Disease-free survival
4. Fracture incidence
5. Osteonecrosis of the jaw (ONJ)
6. Infusion-related side effects

ABC

1. Bone metastases
2. SRE
3. Overall survival
4. Quality of life

BCBM

1. SRE
2. Median time to a SRE
3. Overall survival
4. Bone pain
5. Quality of life

We used GRADEproGDT software (GRADEpro GDT 2015) to develop the 'Summary of findings' tables and followed GRADE guidance (Schünemann 2011b). Two authors (AG & MLW) graded the quality of the evidence for the most recent review update.

To calculate the absolute risk for the control group for time-to-event outcomes, we estimated the event rate at a specific time point (i.e. three-year time point for both overall survival and disease-free survival) from the Kaplan-Meier curves. We entered these estimated values in GRADEpro GDT software, which automatically populated the corresponding absolute risks for the intervention group at the three-year time point.

Subgroup analysis and investigation of heterogeneity

We had planned to conduct subgroup analyses for age, menopausal status, presence of skeletal disease, previous or concomitant chemotherapy, previous or concurrent endocrine therapy, route of administration of drugs, type of bisphosphonate or bone-acting agent and risk groups in early breast cancer (by nodal status, oestrogen/progesterone and HER2 status). However, subgroup analyses were not possible for many pre-planned subgroups because not all studies presented sufficient data to be stratified by these subgroups.

Thus, in the formal analysis, the only pre-planned subgroups we included were route of administration of drugs, type of bisphosphonate or bone-acting agent and menopausal status. For the menopausal status subgroup, some studies specifically recruited premenopausal or postmenopausal women, which enabled us to stratify them in either category. In other studies that recruited both premenopausal and postmenopausal women, we attempted to find out the separate outcomes for each menopausal subgroup. If this was reported, we collated the separate outcomes and analysed them in each subgroup. We were also interested in examining the effect of bisphosphonate in EBC according to the recurrence risk group, especially given the observed discrepancy in results between two large RCTs from two different populations (AZURE 2014 in stage II/III; ABCSG-12 2011 in stage I/II breast cancer). This was not possible since many EBC bisphosphonate studies did not report outcomes stratified by tumour stage or recurrence risk group. This would best be done in a meta-analysis of individual participant data from each study (Colleoni 2000). We did, however, summarise the baseline characteristics of each study that reported the percentage of women who were pre- or postmenopausal at the point of study recruitment, hormone receptor- or oestrogen receptor-positive, and on chemotherapy or endocrine therapy (Table 1).

Sensitivity analysis

For the 2012 and 2016 update, we intended to exclude hypercalcaemia (HCM) from our definition of the total number of SREs, however this was not possible because many studies presented aggregate data for SREs from which it was impossible to subtract the episodes of HCM. We instead chose to perform a sensitivity analysis by evaluating the effect of including or excluding HCM as a primary SRE.

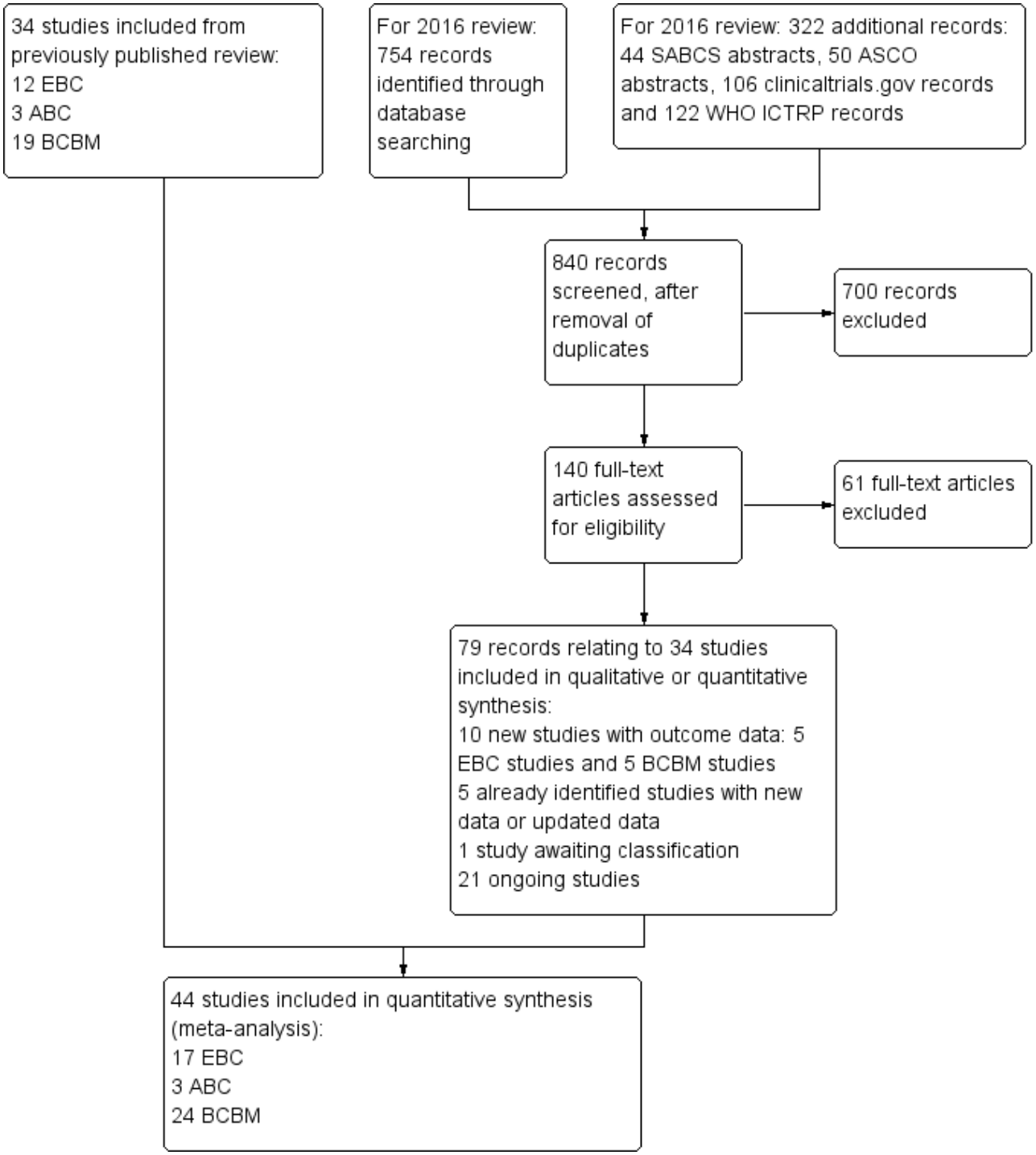
RESULTS

Description of studies

Results of the search

For the 2016 review update, we have outlined the search process in a PRISMA flow diagram (refer to Figure 1) (Moher 2009). We identified 754 records through searching Cochrane Breast Cancer's Specialised Register, CENTRAL, MEDLINE and Embase, and an additional 322 records from searches of ASCO and SABCS conference proceedings, the WHO ICTRP and ClinicalTrials.gov. After duplicate records were excluded, from 840 unique records we excluded 700 records based on review of the abstracts retrieved. We retrieved 140 full-text articles of which we excluded 61 due to not fulfilling the selection criteria. The predominant reasons for exclusion were that studies were not RCTs or were primarily studies of bone density without clinical endpoints such as bone metastases, disease-free survival or overall survival. The remaining 79 records related to 34 studies:

Figure 1. Study flow diagram
ABC: advanced breast cancer; ASCO: American Society of Clinical Oncology; BCBM: breast cancer with bone metastases; EBC: early breast cancer; SABCS: San Antonio Breast Cancer Symposium



1. 10 new studies with outcome data: ABCSG-18 2015; CALGB-70604 2015; GAIN 2013; NATAN 2016; OPTIMIZE-2 2014; SWOG-S0307 2015; von Au 2016; ZICE 2014; ZO-FAST 2013; ZOOM 2013;
2. five previously identified and included studies with new or updated outcome data: Aft 2012; AZURE 2014; ABCSG-12 2011; NSABP-34 2012; Z-FAST 2012;
3. one study awaiting classification: BISMARK 2012; and,
4. 18 ongoing studies, including three newly identified ongoing studies: El-Ibrashi 2016; Jiang 2016; Kummel 2016 (GeparX)

Since the previously published review, the study NCT00320710 has been re-named OPTIMIZE-2 2014 in keeping with published

abstracts, and is now an included study. In addition, some studies have been renamed to incorporate their trial name.

When combining studies from the original review, previous review updates (Pavlakis 2002; Pavlakis 2005; Wong 2012) and the 2016 review update, there were 44 studies included in this updated review (Figure 1). Seventeen studies involved women with early breast cancer (EBC), three studies involved women with advanced breast cancer (ABC) and 24 studies (contributing to 23 treatment comparisons) involved women with advanced disease and bone metastases (BCBM).

The PRISMA flowchart for the original review and previous review updates are located in the previously published version of this review (Wong 2012).

Included studies

Refer to Characteristics of included studies.

Early breast cancer (EBC)

The 17 included studies, involving 26,129 women, contributed to the following treatment comparisons.

1. Bisphosphonate versus placebo/observation: 12 studies (ABCSG-12 2011; Aft 2012; AZURE 2014; Diel 1998; GAIN 2013; Hershman 2008; Kristensen 2008; NATAN 2016; NSABP-34 2012; Powles 2006; Saarto 2004; Tevaarwerk 2007)
2. Denosumab versus placebo: one study (ABCSG-18 2015)
3. Bisphosphonate versus a different bisphosphonate: one study (SWOG-S0307 2015)
4. Immediate versus delayed bisphosphonate (triggered by falling bone mineral density (BMD), minimal trauma or vertebral fracture): three studies (E-ZO-FAST 2012; Z-FAST 2012; ZO-FAST 2013)

Bisphosphonate versus placebo/observation

Five studies evaluated intravenous zoledronate. ABCSG-12 2011 evaluated zoledronate every six months for three years and AZURE 2014 evaluated a tapering regimen of zoledronate over five years. Two studies (Hershman 2008; Tevaarwerk 2007) were primarily studies of BMD that also reported disease recurrence and survival. Aft 2012 measured disseminated tumour cells in bone marrow as its primary endpoint.

Four studies evaluated oral clodronate. Two large, placebo-controlled, phase III RCTs evaluated oral clodronate 1600 mg a day for either two years (Powles 2006) or three years (NSABP-34 2012). Two smaller studies with open-label control arms compared oral clodronate 1600 mg a day for either two years (Diel 1998) or three years (Saarto 2004).

One large, phase III, open-label study (GAIN 2013) in women with node-positive breast cancer and undergoing adjuvant chemotherapy evaluated oral ibandronate. This study was conducted as a 2 x 2 factorial; women were randomised 2:1 to receive oral ibandronate 50 mg a day for two years or observation, with another randomisation 1:1 of two different dose-dense chemotherapy regimens.

One open-label study (Kristensen 2008) of a heterogeneous population of women with predominantly oestrogen receptor (ER)/progesterone receptor (PR)-negative EBC (76%) evaluated oral pamidronate. The study took place between 1990 and 1996 in Scandinavian centres, without adjuvant endocrine therapy, and randomised women to two different chemotherapy regimens. Women were also randomised to oral pamidronate (150 mg a day) or observation. Although oral pamidronate is currently not available for clinical use, the study satisfied 'Risk of bias' assessment and we therefore included it in the meta-analysis.

Denosumab versus placebo

ABCSG-18 2015 conducted a prospective, double-blind, placebo-controlled, phase III trial of postmenopausal women with hormone receptor-positive early breast cancer receiving treatment with aromatase inhibitors. Women were randomised to receive either ongoing subcutaneous denosumab 60 mg or placebo every six months.

Direct comparisons of different bisphosphonate regimens

SWOG-S0307 2015 conducted a phase III, open-label study comparing three bisphosphonates: intravenous zoledronate 4 mg (every four weeks) for six months then once every three months for two-and-a-half years, oral clodronate (1600 mg a day) for three years and oral ibandronate (50 mg a day) for three years in women with stage I to III adenocarcinoma.

Immediate versus delayed bisphosphonate

Three similarly designed, geographically diverse studies explored immediate or delayed zoledronate in postmenopausal women with hormone receptor-positive breast cancer commencing adjuvant treatment with letrozole (E-ZO-FAST 2012; Z-FAST 2012; ZO-FAST 2013). All used common criteria to trigger the commencement of delayed zoledronate: a BMD T-score that decreased to –2.0 (lumbar spine (LS) or total hip (TH)) or non-traumatic fracture. All included primary endpoints of percentage change in the LS BMD at 12 months.

Advanced breast cancer without bone metastases (ABC)

Three included studies, involving 330 women, contributed to the following treatment-comparison.

1. Bisphosphonate versus placebo/observation: three studies (Kanis 1996; Mardiak 2000;Van-Holten 1996)

Two studies were placebo-controlled trials of oral clodronate (Kanis 1996; Mardiak 2000) while the other study was an open-label trial of oral pamidronate (Van-Holten 1996). Kanis 1996 included a study population with recurrent breast cancer without bone metastases. Mardiak 2000 included women with breast cancer with previously untreated, locally advanced disease or extra-skeletal metastases (excluding central nervous system (CNS) metastases). Van-Holten 1996 studied locally advanced disease as well as breast cancer with extra-skeletal metastases.

Metastatic breast cancer with bone metastases (BCBM)

The 24 included studies (25 treatment comparisons), involving 10,853 women, contributed to the following treatment-comparison groups.

1. Bisphosphonate versus placebo/observation:
   a. clodronate: five studies (Elomaa 1983; Kristensen 1999; Martoni 1991; Paterson 1993; Tubiana-Hulin 2001)
   b. pamidronate: four studies (AREDIA 1998; Conte 1996; Hultborn 1999; Van-Holten 1987)
   c. ibandronate: four studies (Body 2003; Body 2004; Heras 2009; Tripathy 2004)
   d. zoledronate: one study (Kohno 2005)
2. Bisphosphonate versus a different bisphosphonate: four studies (Diel 1999; Rosen 2004; von Au 2016; ZICE 2014)
3. Denosumab versus bisphosphonate: three studies (Fizazi 2009; Lipton 2008; Stopeck 2010)
4. Standard versus reduced frequency (every three to four weeks versus every 12 weeks of bone-targeted agents: four studies (CALGB-70604 2015; Fizazi 2009; OPTIMIZE-2 2014; ZOOM 2013)

Bisphosphonate versus placebo/observation

Three studies compared bisphosphonates with no-bisphosphonates control (Conte 1996; Kristensen 1999; Van-Holten 1987). Eleven studies compared bisphosphonates with a placebo control. Of these studies, there were two studies of intravenous pamidronate (AREDIA 1998; Hultborn 1999), three studies of oral clodronate (Elomaa 1983; Paterson 1993; Tubiana-Hulin 2001), one study of intravenous or intramuscular clodronate (Martoni 1991), two of intravenous ibandronate (Body 2003; Heras 2009), two of oral ibandronate (Body 2004; Tripathy 2004) and one of zoledronate in Japanese women only (Kohno 2005).

Bisphosphonate versus different bisphosphonate

Accruing in the 1990s, Diel 1999 (published only as an abstract) and von Au 2016 compared intravenous or oral clodronate to intravenous pamidronate. Accruing in the early 2000s, Rosen 2004 compared intravenous zoledronate to intravenous pamidronate in people with multiple myeloma and women with ABC and clinically evident bone metastases (1648 participants). Separate data for the women with BCBM were provided on request (1130 women) with updated published results available in 2003. ZICE 2014 was a phase III, double-blinded, non-inferiority study comparing oral ibandronate to intravenous zoledronate.

Denosumab versus bisphosphonate

A randomised phase II trial (Lipton 2008) compared differing doses of subcutaneous denosumab every four weeks (30 mg, 120 mg or 180 mg) to the physician's choice of bisphosphonate (zoledronate, pamidronate or ibandronate every four weeks). The phase III trial of denosumab (Stopeck 2010) was a double-blinded, double-dummy trial that compared subcutaneous denosumab 120 mg every four weeks (plus intravenous placebo) versus intravenous zoledronate 4 mg every four weeks (plus subcutaneous placebo). Fizazi 2009 recruited participants with breast cancer, prostate cancer and multiple myeloma, with data from breast cancer subgroups (n = 46) provided from the study sponsor. This randomised phase II, three-armed trial compared 1:1:1 subcutaneous denosumab 180 mg every four weeks; subcutaneous denosumab 180 mg every 12 weeks or intravenous bisphosphonate (physician's choice) with consequently small numbers in each arm.

Standard versus reduced frequency of bone-targeted agents

ZOOM 2013 was a phase III, non-inferiority trial of women with BCBM who had completed 12 to 15 months of zoledronate every four weeks, then randomised to zoledronate 4 mg every four weeks or every 12 weeks. As described above, the randomised phase II trial conducted by Fizazi 2009 included a small number of women who were given either denosumab or bisphosphonate. CALGB-70604 2015 was a phase III open-label study of participants with metastatic breast cancer, prostate or multiple myeloma involving bone. Participants were randomised to receive either zoledronate 4 mg every four weeks or 12 weeks for up to two years. OPTIMIZE-2 2014 was a randomised, phase III double-blind study comparing zoledronate 4 mg every four weeks to every 12 weeks in women with bone metastases from breast cancer.

Studies awaiting classification

The BISMARK 2012 study reported results in a 2012 abstract. The comparator group included either intravenous zoledronate every 15 to 16 weeks, 8 to 9 weeks or 3 to 4 weeks. As data were not reported separately for each of these schedules, we were unable to include the data from this study by comparing the standard intervention group (zoledronate intravenous every 3 to 4 weeks) to the reduced-frequency group (either 16 to 15 weeks or 8 to 9 weeks). We await data from the complete trial publication.

Ongoing studies

We identified 18 ongoing studies (Figure 1) through database searches of the WHO ICTRP, ClinicalTrials.gov and contacting sponsors (Novartis Oncology and Amgen Oncology). Given the large number of ongoing studies, we only included RCTs reporting a primary endpoint of interest (SREs, recurrence or survival) in the Characteristics of ongoing studies table.

Excluded studies

The 19 excluded studies are listed in the Characteristics of excluded studies section.

Notably, a subset of the studies excluded are listed. We did not include three studies on risedronate and EBC. Hines 2009 was a BMD study randomising women to risedronate or placebo for one year but no SRE endpoints were discussed. Greenspan 2008 was another BMD study that randomised women to risedronate or placebo for two years. The authors reported no difference in recurrence between the two arms but have not explicitly expanded quantitatively or qualitatively on this. Likewise, Delmas 1997, also randomised women to risedronate or placebo for two years. The text mentioned that two women had died from recurrent breast cancer but no information was given about the type of recurrence that these women had had, total recurrence or overall death rate. Hence, we did not include any of the risedronate studies.

Saarto 2005 was a histological study describing the effect of adjuvant clodronate on bone biopsies obtained from a small subset (n = 63) of consenting women within an included adjuvant study by Saarto 2001. No additional clinical outcomes were reported. Scotti 2014 (BONADIUV) was a single-blind, randomised, placebo-controlled phase II study designed to evaluate the impact of oral ibandronate (150 mg monthly) on BMD in osteopenic women receiving aromatase inhibitors in the adjuvant setting. The study evaluated BMD, safety and tolerability endpoints only. Sestak 2014 (IBIS-II) was a bone substudy of the multi-national IBIS-II primary prevention trial of anastrozole reporting primary endpoints of BMD only.

Risk of bias in included studies

Refer to Figure 2 for a summary of the risk of bias judgements for each 'Risk of bias' domain of the included studies.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

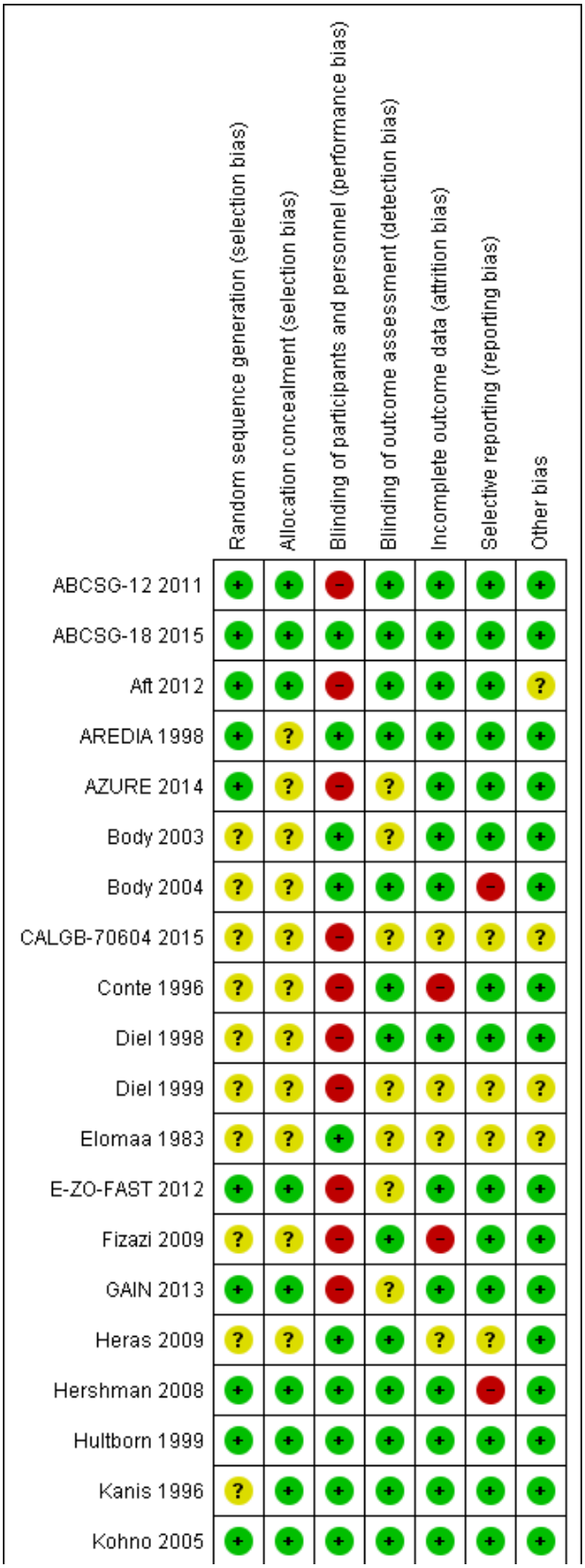
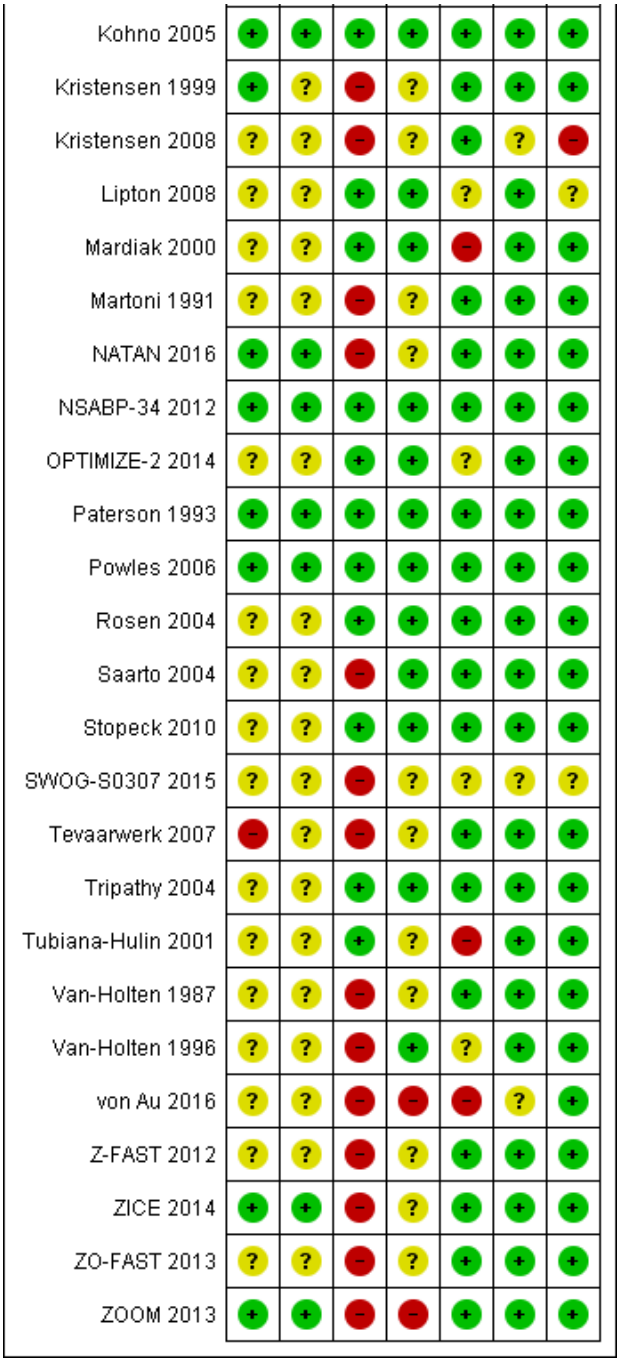


Figure 2. (Continued)



Allocation

The 44 studies were described as randomised. If the study adequately described the method of random sequence generation and the baseline characteristics in each treatment arm of a study were balanced, we categorised the study to be at low risk of bias. We deemed 17 studies to be at low risk of bias. It was not possible to accurately assess the randomisation process in 26 studies owing to the lack of information presented in the trial publications; we classified these 26 studies as having an unclear risk of bias. One study (Tevaarwerk 2007) had significant imbalances between the baseline characteristics in each treatment arm and we assumed that the randomisation process was inadequate for this study. There was more T1 disease in the treatment group compared to control (39% versus 2%) and more N2-3 disease in the control group compared to treatment (81% versus 56%). This means that there were more women in the control group having disease with intermediate or high-risk of recurrence than in the treatment group. Therefore, we classified this study at high risk of bias.

Fifteen studies out of 44 studies were at low risk of bias for allocation concealment. Twenty-nine studies did not describe methods of allocation concealment or in sufficient details in the trial publication and we judged them as having unclear risk of bias.

Blinding

Blinding of participants and personnel

Nineteen studies were labelled as double-blind or double-dummy design and we judged them to be at low risk of bias. A proportion of studies that compared bisphosphonates to usual care were open label and not placebo-controlled. In addition, studies comparing bisphosphonates of different routes of administration (intravenous versus oral) or administration schedules were often not adequately controlled. Performance bias owing to the lack of blinding of participants and personnel could not be ruled out in these cases and therefore we classified 25 studies as being at high risk of bias.

Blinding of outcome assessors

We judged 24 studies to be at low risk of bias. Eighteen studies did not provide any information about blinding of outcome assessment. As outcomes included composite endpoints such as SREs, we judged these 18 studies to be at unclear risk of bias. We judged two studies (von Au 2016; ZOOM 2013) to be at high risk of bias for stating that no one involved in the trial was masked to treatment allocation.

Incomplete outcome data

Thirty-one studies provided either well-described CONSORT flow diagrams (Schultz 2010) or complete outcome data sets, and conducted intention-to-treat analyses. We judged these studies to be at low risk of bias. Five studies were at high risk of bias owing to a lack of intention-to-treat analysis or high dropout rate, or both, with little information on whether the dropouts were different between treatment and comparator arms. The remaining eight studies were at unclear risk of bias due to insufficient information provided in the abstract or trial publication on missing outcome data.

Selective reporting

Thirty-five studies complied with reporting criteria by either reporting results for those outcomes listed in the methods section of the trial publication or listing a trial registration record with the listed outcomes found in the methods and results section of the trial publication. We assessed these studies to be at low risk of bias. Seven studies provided either insufficient detail about the primary or secondary endpoints or did not provide a complete list of the adverse events as expected. We categorised these studies at unclear risk of bias. Two studies were at high risk of bias for failing to report data for one treatment group (i.e. ibandronate 20 mg data; Body 2004) or adding a new outcome (i.e. recurrence; Hershman 2008).

Other potential sources of bias

Thirty-seven studies were generally free of other sources of bias. We judged one study (Kristensen 2008) to be at high risk of bias due to not permitting women to be on endocrine therapy when 17% of participants in the control arm versus 13% in the pamidronate arm were oestrogen receptor-positive. This may potentially bias results against the control arm since these participants were not treated optimally. The remaining six studies we judged to be at unclear risk of bias due to very little information in the abstract or trial publication to adequately assess whether the trial was free of other sources of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Bisphosphonates compared to placebo/observation for women with early breast cancer; **Summary of findings 2** Bisphosphonates compared to placebo/observation for women with advanced breast cancer without bone metastases; **Summary of findings 3** Bisphosphonates compared to placebo/observation for women with metastatic breast cancer and bone metastases

Early breast cancer (EBC)

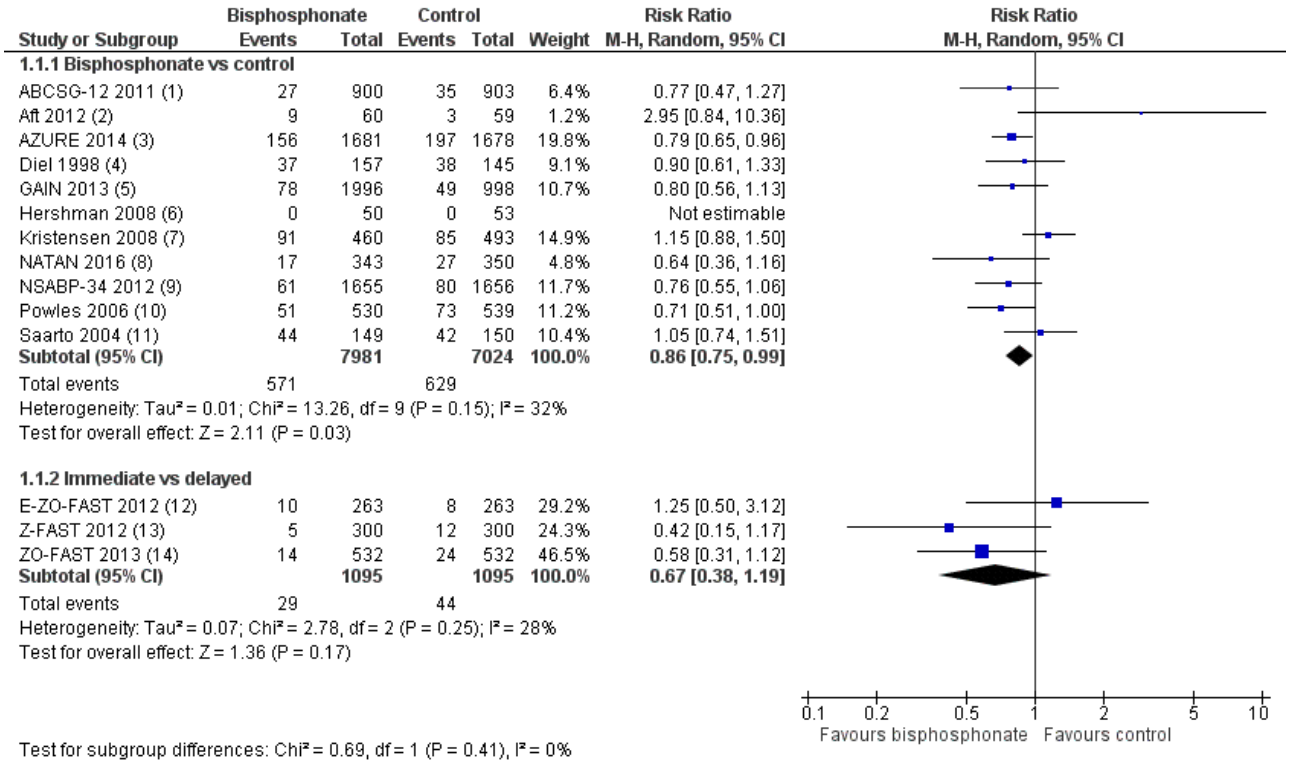
There were 17 included studies: 12 studies compared bisphosphonates to placebo/observation, one study tested denosumab against placebo, one study compared three different bisphosphonates and three studies examined immediate versus delayed administration of bisphosphonates. However at present data are not mature for the study evaluating denosumab (ABCSG-18 2015) and very few data were available from one study examining zoledronate (Tevaarwerk 2007) and another study comparing different bisphosphonates (SWOG-S0307 2015). The majority of studies treated women with intravenous zoledronate (n = 10,361 women) or oral clodronate (n = 7132 women). The baseline characteristics of participants in each study are summarised in Table 1.

Bone metastases

Bisphosphonate versus placebo/no bisphosphonate

Bisphosphonates were associated with a reduced risk of bone metastases compared to control (RR 0.86, 95% CI 0.75 to 0.99; 11 studies; I^2 = 32%, P = 0.03; Analysis 1.1 (subtotal 1.1.1); moderate-quality evidence). There were 1200 events in 15,005 women randomised (Figure 3).

Figure 3. Forest plot of comparison: 3 Early breast cancer (EBC), outcome: 3.1 Incidence of bone metastases in EBC: bisphosphonate versus control



Intravenous bisphosphonate versus control

Intraveous zoledronate versus control

Eight studies examined intravenous zoledronate (e.g. 4 mg every three to four weeks or every three to six months for over one to five years, or upfront schedule over five years) compared to placebo/observation or delayed administration of zoledronate. Intravenous zoledronate was associated with a reduced risk of bone metastases compared to control (RR 0.77, 95% CI 0.60 to 0.99; P = 0.04; Analysis 1.2) and there was no significant heterogeneity (I^2 = 25%, P = 0.24). There were 544 events in 8267 randomised women.

Oral bisphosphonate versus placebo/observation

Oral clodronate versus placebo/observation

Four studies compared oral clodronate (1600 mg daily for two to three years) compared to control. Clodronate appeared to provide some benefit on preventing bone metastases compared to placebo/no bisphosphonate (RR 0.84, 95% CI 0.70 to 1.00; P = 0.05; Analysis 1.2). We observed no heterogeneity. There were 426 events in 4981 women randomised.

Oral pamidronate versus placebo

One study compared oral pamidronate (150 mg twice a day for four years) to placebo. The RR was 1.15 (95% CI 0.88 to 1.50; Analysis 1.2). There were 176 events in 953 women randomised.

Oral ibandronate versus observation

One study compared oral ibandronate (50 mg daily for two years) to observation. The RR was 0.80 (95% CI 0.56 to 1.13; Analysis 1.2). There were 127 events in 2994 women randomised.

Denosumab versus placebo

Data for this outcome have been collected by ABCSG-18 2015 but are yet to be published.

Immediate versus delayed bisphosphonate

The incidence of bone metastases did not differ significantly between immediate and delayed administration of bisphosphonates (RR 0.67, 95% 0.38 to 1.19; 3 studies; Analysis 1.1) however the confidence intervals were wide. There was no significant heterogeneity (I^2 = 28%, P = 0.25). There were 73 events in 2190 women randomised. The three studies comparing immediate versus delayed bisphosphonates were BMD studies (E-ZO-FAST 2012; Z-FAST 2012; ZO-FAST 2013) that were only powered to study the effects of bisphosphonates on BMD and not the prevention of bone metastases or recurrence.

Visceral metastases

Bisphosphonate versus placebo/observation

The incidence of visceral metastases did not differ significantly between bisphosphonates and placebo/observation (RR 1.04, 95% CI 0.92 to 1.18; P = 0.50; 10 studies; Analysis 1.3 (subtotal 1.3.1)) and no significant heterogeneity (I^2 = 24%, P = 0.22). There were 1267 events in 14,902 women randomised.

Denosumab versus placebo

No data for this outcome.

Immediate versus delayed bisphosphonate

The incidence of visceral metastases did not differ significantly between immediate and delayed administration of bisphosphonates however the confidence interval was very wide (RR 0.85, 95% CI 0.46 to 1.60; P = 0.62; 3 studies; Analysis 1.3 (subtotal 1.3.2), no significant heterogeneity (I^2 = 25%, P = 0.27)). There were 59 events in 2190 women randomised.

Locoregional recurrence

Bisphosphonate versus placebo/observation

Locoregional recurrence did not differ significantly between bisphosphonates and placebo/observation (RR 1.01, 95% CI 0.85 to 1.20; P = 0.89; 8 studies; Analysis 1.4 (subtotal 1.4.1)) and no significant heterogeneity (I^2 = 26%, P = 0.22). There were 755 recurrences in 13,531 women.

Denosumab versus placebo

No data for this outcome.

Immediate versus delayed bisphosphonate

Locoregional recurrence did not differ significantly between immediate and delayed administration of bisphosphonates however the confidence interval was very wide (RR 1.08, 95% CI 0.26 to 4.48; P = 0.92; 3 studies; Analysis 1.4 (subtotal 1.4.2)) and there was moderate heterogeneity (I^2 = 51%, P = 0.13). In these three studies, there were 25 recurrences in 2190 women randomised.

Recurrence (locoregional and distant recurrence)

Bisphosphonate versus placebo/observation

Overall recurrence did not differ significantly between groups with a RR of 1.00 (95% CI 0.89 to 1.13; P = 0.95; 11 studies; Analysis 1.5 (subtotal 1.5.1)). There was significant heterogeneity (I^2 = 68%, P = 0.001). In total, there were 3034 recurrences in 15,005 women randomised.

Denosumab versus**placebo**

No data for this outcome.

Immediate versus delayed bisphosphonate

Overall recurrence did not differ significantly between immediate and delayed bisphosphonates with a RR of 0.87 however the confidence interval was wide (95% CI 0.52 to 1.46; P = 0.60; 3 studies; Analysis 1.5 (subtotal 1.5.2)). There was considerable heterogeneity (I^2 = 58%, P = 0.09). There were 153 recurrences in 2191 women.

Intravenous or oral bisphosphonates versus control

When comparing the different bisphosphonate groups (i.e. zoledronate, immediate administration of zoledronate, clodronate, pamidronate or ibandronate) to their respective control (i.e. placebo, observation or delayed administration of zoledronate), overall recurrence did not differ significantly (Analysis 1.6).

For zoledronate studies versus control: RR = 0.97 (95% CI 0.76 to 1.23; P = 0.78; 8 studies; 8268 women); clodronate versus control: RR = 1.00 (95% CI 0.84 to 1.19; P = 0.98; 4 studies; 4981 women); pamidronate versus control: RR = 1.08 (95% CI 0.94 to 1.24; P = 0.27; 1 study; 953 women) and ibandronate versus control: RR = 1.00 (95% CI 0.82 to 1.22; P = 1.00; 1 study; 2994 women). There was substantial heterogeneity across the zoledronate (I^2 = 76%, P < 0.001) and clodronate studies (I^2 = 55%, P = 0.08).

Overall survival

Bisphosphonate versus placebo/observation

Five study authors provided unpublished data in various formats (Aft 2012; AZURE 2014; GAIN 2013; Kristensen 2008; NATAN 2016).

In the analysis using time-to event data, data were available from nine out of the 12 studies. There was an benefit from bisphosphonates compared to placebo/observation with a HR of 0.91 (95% CI 0.83 to 0.99; P = 0.04; 13,949 women; Analysis 1.7 (Figure 4), subtotal 1.13.1; high-quality evidence; funnel plot: Figure 5) with some heterogeneity (I^2 = 39%, P = 0.11). In the analysis using dichotomous data, data on overall survival were available from 10 out of the 12 studies. Overall survival did not differ significantly between bisphosphonates and placebo/observation with a RR of 0.91 (95% CI 0.80 to 1.03; P = 0.14; 14,902 women; Analysis 1.8, subtotal 1.14.1). There were 2394 deaths in 14,902 women randomised. Heterogeneity was substantial across these studies (I^2 = 66%, P = 0.002).

Figure 4. Forest plot of comparison: 1 Early Breast Cancer (EBC), outcome: 1.7 Overall survival: time-to-event outcome.

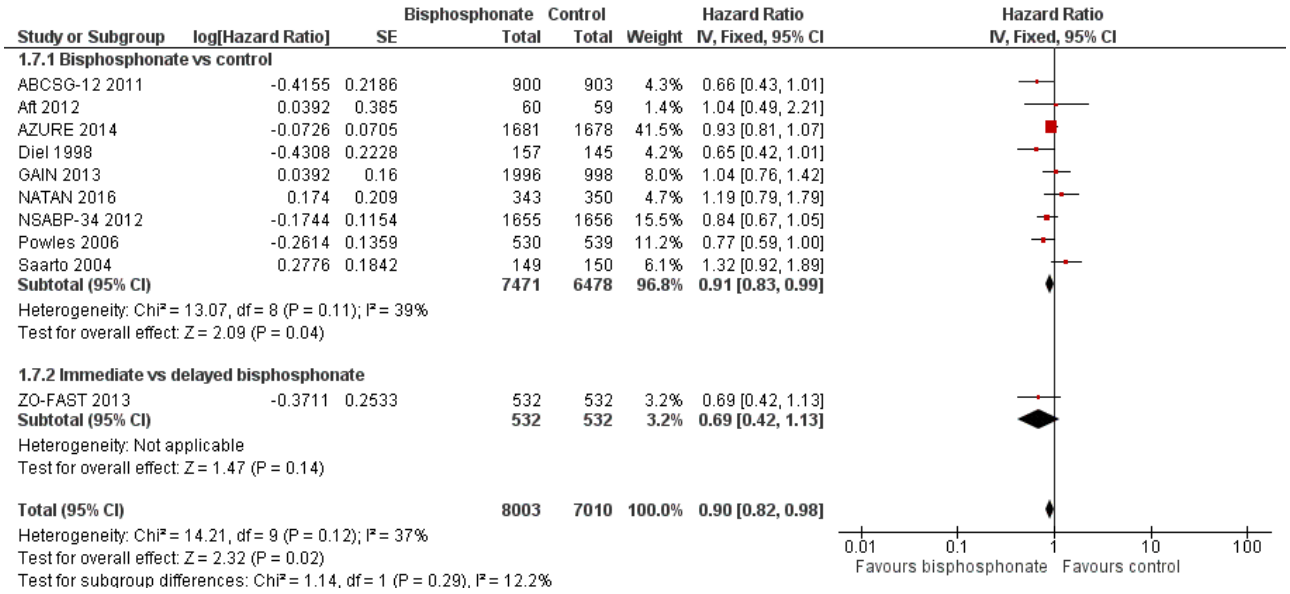
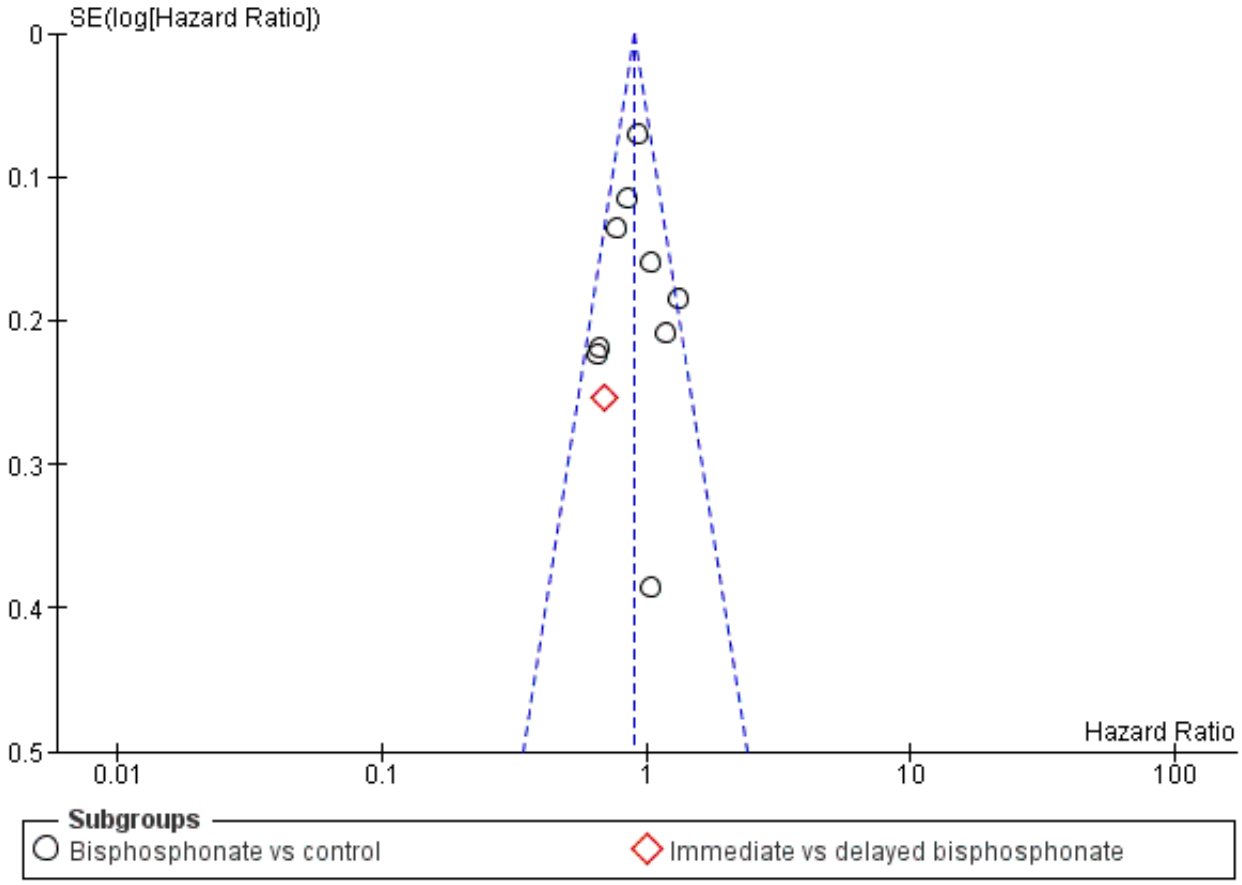


Figure 5. Funnel plot of comparison: 1 Early Breast Cancer (EBC), outcome: 1.7 Overall survival: time-to-event outcome.



Denosumab versus placebo

Data for this outcome have been collected by ABCSG-18 2015 but are yet to be published.

Immediate versus delayed bisphosphonate

In the analysis using time-to-event data, data from only one study were available (ZO-FAST 2013) with the HR of 0.69 (95% CI 0.42 to 1.13; 1064 women; Analysis 1.7, subtotal 1.13.2). In the analysis using dichotomous data, information on overall survival were available from two out of the three studies. Overall survival did not differ significantly between immediate bisphosphonates and delayed treatment with a RR of 2.14 however with very wide confidence intervals (95% CI 0.69 to 6.60; Analysis 1.8, subtotal 1.14.2; no heterogeneity). There were 14 deaths in 1126 women randomised.

Intravenous or oral bisphosphonates versus control

Intravenous zoledronate versus control

In the analysis using time-to-event data, intravenous zoledronate did not appear to provide a benefit in overall survival compared to placebo/delayed zoledronate (HR 0.91; 95% CI 0.81 to 1.03; P = 0.13; 5 studies; 7038 women; I^2 = 23%, P = 0.27; Analysis 1.9). This result was confirmed when analysing data as dichotomous outcomes with a RR of 0.94 (95% CI 0.80 to 1.11; P = 0.45; 6 studies; I^2 = 26%, P = 0.24; Analysis 1.10). There were 980 deaths in 7100 women randomised. In addition, if the Z-FAST 2012 or ZO-FAST 2013 study was removed from the time-to-event or dichotomous data analyses due to involving delayed bisphosphonate in the control arm, the non-significant finding persisted in these two analyses.

Oral clodronate versus placebo/observation

Data were available from all four studies. In the analysis of time-to-event outcome, there was a benefit from clodronate compared to placebo/observation with a HR of 0.86 (95% CI 0.74 to 0.99; P = 0.04; 4981 women; Analysis 1.9) with significant heterogeneity (I^2 = 61%, P = 0.05). In the analysis of dichotomous data, overall survival did not differ significantly between clodronate and placebo/observation with a RR of 0.80 (95% CI 0.60 to 1.06; P = 0.12; Analysis 1.10) with considerable heterogeneity (I^2 = 78%, P = 0.004). There were 744 deaths in 4981 women randomised.

Oral pamidronate versus observation

One study compared pamidronate to observation and there appeared to be no effect of pamidronate on overall survival (RR 1.06, 95% CI 0.94 to 1.20; P = 0.32; 1 study; Analysis 1.10). There were 498 deaths in 953 women randomised.

Oral ibandronate versus observation

One study compared ibandronate to observation with the hazard ratio reported in the trial publication as 1.04 (95% CI 0.76 to 1.42; P = 0.81; Analysis 1.9). This result was confirmed using dichotomous data (RR 1.10, 95% CI 0.82 to 1.49; P = 0.52; 1 study; Analysis 1.10). There were 186 deaths in 2994 women randomised.

Direct comparisons of different bisphosphonate regimens

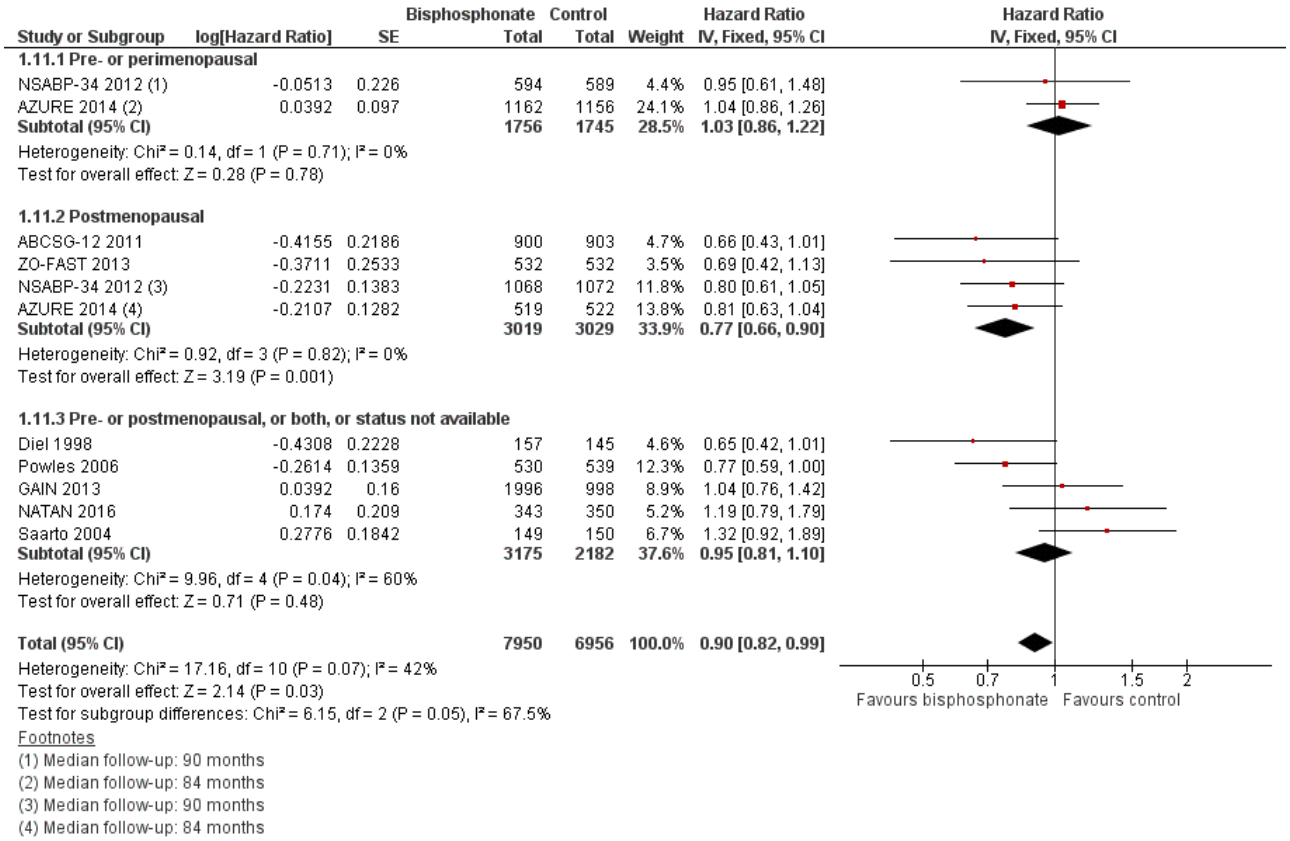
Data from one three-arm study (SWOG-S0307 2015), comparing zoledronate intravenous, oral clodronate and oral ibandronate, reported that overall survival was 93% in all three groups.

Menopausal status

Five study authors provided unpublished data based on menopausal status (Aft 2012; AZURE 2014; GAIN 2013; Kristensen 2008; NATAN 2016).

For the analysis using time-to-event data, two studies provided data specifically on pre- or perimenopausal women, four studies on postmenopausal women and five studies categorised as including pre- or postmenopausal women or menopausal status unknown. There was a benefit from adjuvant or immediate bisphosphonates in postmenopausal women (HR 0.77, 95% CI 0.66 to 0.90; P = 0.001; 4 studies; 6048 women; no heterogeneity; high-quality evidence; Analysis 1.11, subtotal 1.17.2) while there was evidence of no effect of bisphosphonates in premenopausal women (HR 1.03, 95% CI 0.86 to 1.22; P = 0.78; 2 studies; 3501 women; no heterogeneity; high-quality evidence; Analysis 1.11, subtotal 1.17.1) or where study data were not reported separately based on menopausal status (HR 0.95, 95% CI 0.81 to 1.10; P = 0.48; no significant heterogeneity I^2 = 42%, P = 0.07; Analysis 1.11, subtotal 1.17.3). The test for subgroup differences was significant (P = 0.05). If the study examining immediate versus delayed bisphosphonates (ZO-FAST 2013) was removed from the analysis for postmenopausal women due to the delayed bisphosphonate not being a pure control comparison, the treatment effect still persisted using time-to-event data (HR 0.78, 95% CI 0.66 to 0.92; P = 0.004; 3 studies; 4984 women) (Figure 6).

Figure 6. Forest plot of comparison: 1 Early Breast Cancer (EBC), outcome: 1.11 Overall survival by menopausal status: time-to-event outcome.



For the analysis using dichotomous data, six studies provided data specifically on pre- or perimenopausal women, nine studies on postmenopausal women and three studies were categorised as including pre- or postmenopausal women or menopausal status unknown. There appeared to be no effect of adjuvant bisphosphonates in postmenopausal women (RR 0.90, 95% CI 0.78 to 1.03; P = 0.14; 8150 women; no significant heterogeneity; Analysis 1.12, subtotal 1.18.2), pre- or perimenopausal women (RR 1.06, 95% CI 0.96 to 1.18; P = 0.26; 6191 women; no heterogeneity; Analysis 1.12, subtotal 1.18.1) or in studies where data on menopausal status were combined or unknown (RR 0.78, 95% CI 0.50 to 1.20; P = 0.26; 1670 women; significant heterogeneity I^2 = 85%, P = 0.001; Analysis 1.12, subtotal 1.18.3). The test for subgroup differences was not significant (P = 0.09). If the studies examining immediate versus delayed bisphosphonates (E-ZO-FAST 2012; Z-FAST 2012) were removed from the analysis of postmenopausal women, the treatment effect remained non-significant (P = 0.09) with a RR of 0.89 (95% CI 0.78 to 1.02; 7 studies; 7024 women).

One study that compared different bisphosphonates (SWOG-S0307 2015) reported no evidence of treatment differences based on menopausal status.

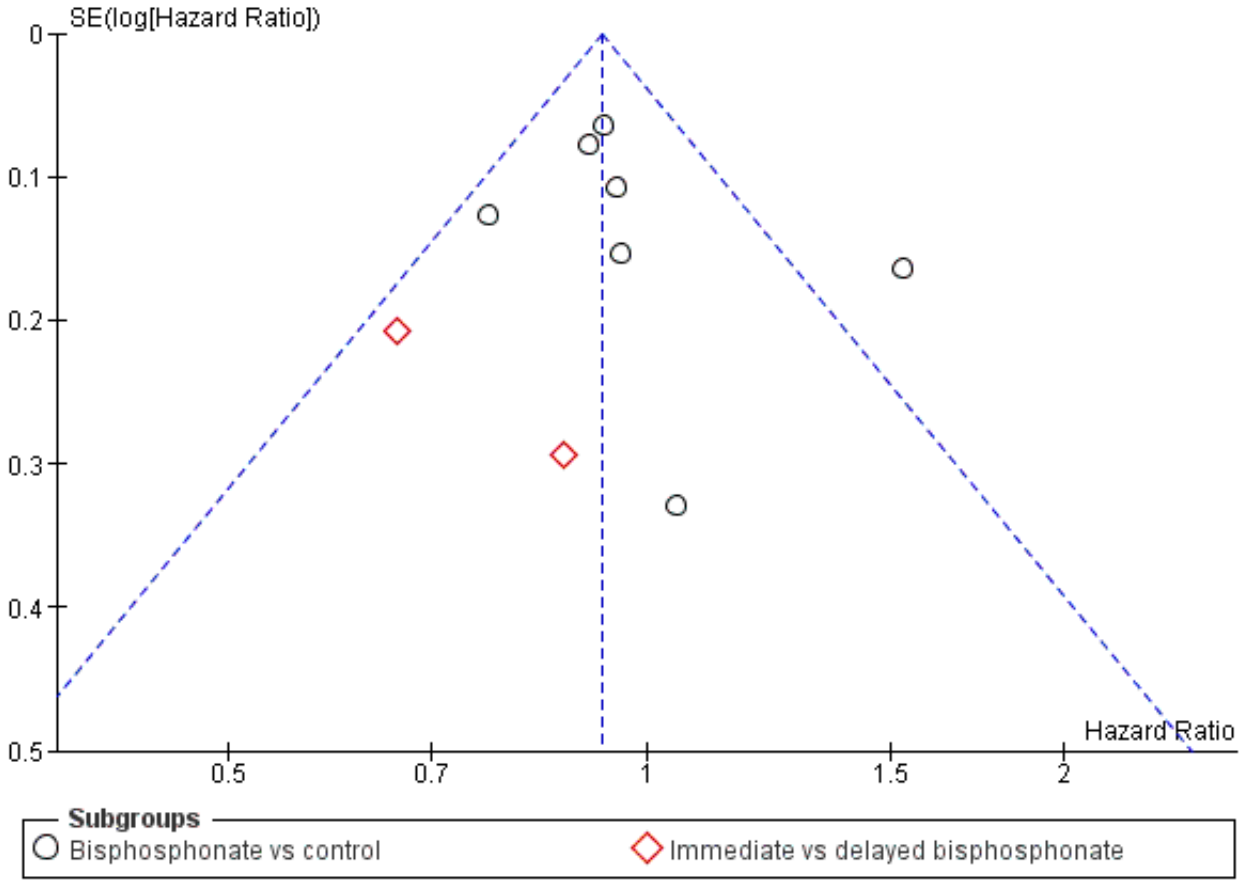
Disease-free survival

Bisphosphonate versus placebo/observation

Five study authors provided unpublished data (Aft 2012; AZURE 2014; GAIN 2013; Kristensen 2008; NATAN 2016).

In the analysis using time-to-event data, data were available from seven out of the 12 studies. There was no observed benefit from bisphosphonates compared to placebo/observation with a HR of 0.94 (95% CI 0.87 to 1.02; P = 0.13; 12,578 women; Analysis 1.13; subtotal 1.7.1; high-quality evidence; funnel plot: Figure 7) and heterogeneity was apparent across studies (I^2 = 49%, P = 0.07). In the analysis using dichotomous data, information on disease-free survival was available from eight out of the 12 studies. Disease-free survival did not differ significantly between bisphosphonates and placebo/observation with a RR of 0.97 (95% CI 0.89 to 1.06; P = 0.47; Analysis 1.14; subtotal 1.8.1). There were 3116 women who progressed out of 13,538 randomised. Heterogeneity was apparent across these studies (I^2 = 48%, P = 0.06).

Figure 7. Funnel plot of comparison: 1 Early Breast Cancer (EBC), outcome: 1.13 Disease-free survival: time-to-event outcome.



Denosumab versus placebo

Data for this outcome have been collected by ABCSG-18 2015 but are yet to be published.

Immediate versus delayed bisphosphonate

In the analysis using time-to-event data, data were available from two out of the three studies. Overall, there was a trend towards a disease-free survival benefit from upfront bisphosphonates compared to delayed bisphosphonates with a HR of 0.72 (95% CI 0.52 to 1.01, P = 0.06; 2 studies; 1664 women; Analysis 1.13; subtotal 1.7.2) with no heterogeneity. Using dichotomous data, a similar trend was observed with a RR of 0.75 (95% CI 0.55 to 1.02; P = 0.06; Analysis 1.14; subtotal 1.8.2) with no heterogeneity. There were 152 women who progressed out of 1664 randomised.

Intravenous or oral bisphosphonates versus control

Intravenous zoledronate versus control

Data were available for six out of the nine studies. In the analysis of time-to-event data, intravenous zoledronate was associated with improved disease-free survival compared to placebo/delayed zoledronate (HR 0.89; 95% CI 0.80 to 0.98; P = 0.02; 7638 women; Analysis 1.15) with no heterogeneity. This result was confirmed when analysing data as dichotomous outcomes with a RR of 0.88 (95% CI 0.79 to 0.98; P = 0.02; 6 studies; Analysis 1.16) and there was no significant heterogeneity (I^2 = 17%, P = 0.30). There were 1685 women who progressed out of 7638 randomised. If the two studies examining immediate versus delayed bisphosphonates (Z-FAST 2012; ZO-FAST 2013) were removed from these analyses due to not strictly conforming to the bisphosphonates versus control comparison, the treatment effect still persisted when using dichotomous data though it became non-significant (at P = 0.06) with time-to-event data (HR 0.91, 95% CI 0.82 to 1.01; 4 studies; 5974 women).

Oral clodronate versus placebo/observation

Data were available for two out the four studies. In the analysis of time-to-event data, oral clodronate did not improve disease-free survival compared to placebo/observation (HR 1.00, 95% CI 0.87 to 1.15; P = 0.97; 2 studies; 3610 women; I^2 = 88%, P = 0.004; Analysis 1.15). This result was confirmed when analysing data as dichotomous outcomes (RR 1.02; 95% CI 0.79 to 1.32; P = 0.86; 2 studies; I^2 = 72%, P = 0.06; Analysis 1.16). There were 746 women who progressed out of 3617 randomised.

Oral pamidronate versus observation

One study compared oral pamidronate to observation. Pamidronate did not improve disease-free survival compared to control (RR 1.12, 95% CI 0.98 to 1.29; P = 0.10; 953 women; Analysis 1.16). There were 432 women who progressed out of 953 women.

Oral ibandronate versus observation

One study compared oral ibandronate to control and ibandronate did not improve disease-free survival compared to observation (HR 0.95, 95% CI 0.77 to 1.17, P = 0.63; Analysis 1.15). This result was confirmed using dichotomous data (RR 1.00, 95% CI 0.83 to 1.21; P = 1.00; 1 study, 2994 women; Analysis 1.16).

Direct comparisons of different bisphosphonate regimens

Data from one three-armed study (SWOG-S0307 2015), comparing intravenous zoledronate, oral clodronate and oral ibandronate, reported that disease-free survival did not differ across groups (P = 0.71). Five-year disease-free survival was 88% in the zoledronate and clodronate groups and 87% in the ibandronate group.

Menopausal status

Five study authors provided unpublished data based on menopausal status in various formats (Aft 2012; AZURE 2014; GAIN 2013; Kristensen 2008; NATAN 2016). For the analysis using time-to-event data, four studies provided data specifically on pre- or perimenopausal women, seven studies on postmenopausal women and one study was categorised as including pre- or postmenopausal women or menopausal status unknown. There was a benefit from adjuvant or immediate bisphosphonates in postmenopausal women (HR 0.82, 95% CI 0.74 to 0.91; P < 0.001; 8314 women; no heterogeneity; high-quality evidence; Analysis 1.17, subtotal 1.11.2) while no benefit was observed in premenopausal women (HR 1.01, 95% CI 0.90 to 1.13; P = 0.84; 5493 women; no heterogeneity; high-quality evidence; Analysis 1.17, subtotal 1.11.1). In the one study where data on menopausal status were combined, there was an apparent increased risk of disease-free survival events in the bisphosphonates arm (Saarto 2004; HR 1.53, 95% CI 1.11 to 2.11; 299 women; P = 0.009; Analysis 1.17, subtotal 1.11.3). The test for subgroup differences was significant (P = 0.0002). If the study examining immediate versus delayed bisphosphonates (Z-FAST 2012) was removed from the analysis for postmenopausal women due to not strictly conforming to the bisphosphonates versus control comparison, the treatment benefit still persisted using time-to-event data (HR 0.83, 95% BCI 0.74 to 0.93; 5 studies; 6650 women).

For the analysis using dichotomous data, new data were added from Aft 2012 and Kristensen 2008 for women who were pre- or postmenopausal. Similar to the time-to-event analysis, there was an observed benefit of adjuvant bisphosphonates in postmenopausal women (RR 0.86; 95% CI 0.77 to 0.97; P = 0.02; 8 studies; 6536 women; Analysis 1.18, subtotal 1.12.2) with no significant heterogeneity across studies (I^2 = 31%, P = 0.18). There appeared to be no effect of adjuvant bisphosphonates in pre- or perimenopausal women (RR 1.05, 95% CI 0.96 to 1.15, P = 0.31; 5 studies; 4997 women; no heterogeneity; Analysis 1.18, subtotal 1.12.1) or in studies where data on menopausal status were combined or unknown (RR 1.02, 95% CI 0.79 to 1.32; P = 0.86; 2 studies; 3617 women; Analysis 1.18, subtotal 1.12.3). The test for subgroup differences was significant (P = 0.04). If the studies examining immediate versus delayed bisphosphonates (Z-FAST 2012; ZO-FAST 2013) were removed from the analysis of postmenopausal women, the treatment effect did not reach statistical significance (P = 0.06) with a RR of 0.88 (95% CI 0.77 to 1.00; 6 studies; 4872 women).

One study that compared different bisphosphonates (SWOG-S0307 2015) reported no evidence of treatment differences based on menopausal status.

Fracture incidence

Bisphosphonate versus placebo/observation

Overall, bisphosphonates did not significantly reduce the incidence of fractures when compared to placebo/observation with a RR of 0.77 (95% CI 0.54 to 1.08; P = 0.13; 6 studies; Analysis 1.19 (subtotal 1.19.1); moderate-quality evidence due to wide confidence intervals). There were 385 events in 7602 women randomised. There was moderate heterogeneity (I^2 = 48%, P = 0.10).

Denosumab versus placebo

Fracture incidence was reduced with denosumab (60 mg sc every 6 months) compared to placebo with a RR of 0.52 (95% CI 0.41 to 0.67; 1 study; Analysis 1.19 (subtotal 1.19.2)). There were 268 events in 3420 women randomised.

Direct comparisons of different bisphosphonate regimens

Based on one study, there was no significant difference in fracture incidence between the different bisphosphonates. There were 94 fractures in 2094 randomised participants (4.5%) in the zoledronate group, 103 fractures in 2151 randomised women (4.8%) in the clodronate group and 62 fractures in the 1507 women randomised (4.1%) in the ibandronate group.

Immediate versus delayed bisphosphonate

Fracture incidence did not appear to differ significantly when comparing immediate and delayed bisphosphonates however the confidence intervals were wide (RR 0.81, 95% CI 0.57 to 1.13; P = 0.21; 3 studies; no heterogeneity; Analysis 1.19 (subtotal 1.19.3)). There were 126 events in 2190 women.

Quality of life

None of the studies collected and reported data on quality of life.

Adverse, drug-related events or toxicity

We have described specific toxicities in detail by treatment comparison in Table 2 and Table 3. In general, few serious adverse events were reported. For the purpose of this section, we have provided a brief narrative summary.

Trial publications frequently collected data on osteonecrosis of the jaw (ONJ; 12 out of 16 studies), renal dysfunction (10 out of 12 studies), drug-related death (10 out of 12 studies) and fever (9 out of 12 studies). Other adverse events were collected such as infusion-type side effects incorporating nausea (7 studies), fatigue (7 studies) and influenza-type symptoms (4 studies), and hypocalcaemia (3 studies).

The zoledronate studies reported between 0 and 26 ONJ cases in each arm of each trial. In AZURE 2014, there were 17 confirmed cases of ONJ and nine suspected cases of ONJ in the intervention arm (zoledronate) against no cases of ONJ in the control arm (Table 2). Overall, the incidence of ONJ was less than 0.5% in the bisphosphonates groups (high-quality evidence). Intravenous bisphosphonates (zoledronate) appeared to slightly increase the incidence of fever, fatigue and nausea compared to placebo however the reporting of the grade of

toxicity often was unspecified. The quality of evidence for infusion-related side-effects was considered to be moderate. Of the bisphosphonates administrated intravenously, the two zoledronate studies (ABCSG-12 2011; NATAN 2016) reported incidences of a cutaneous reaction in both the bisphosphonate and control groups. The number of cutaneous reactions in the one study examining denosumab were the same in both the intervention and control groups. There were no apparent differences in the adverse events between immediate and delayed bisphosphonate studies.

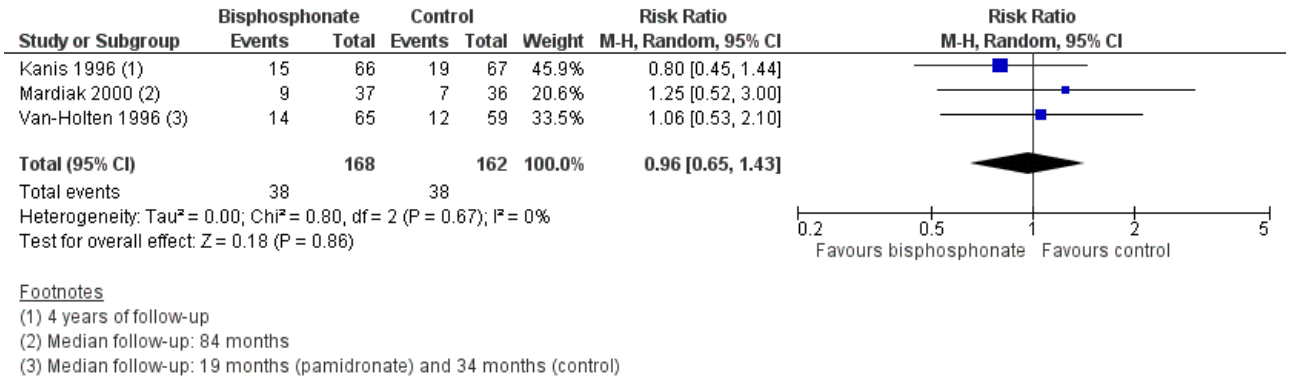
Advanced breast cancer without bone metastases (ABC)

Three studies, involving 330 women, evaluated bisphosphonates compared to placebo in women with ABC without clinically evident bone metastases. Oral clodronate at 1600 mg a day was evaluated in two placebo-controlled studies (Kanis 1996: clodronate taken for three years, women observed for four years; Mardiak 2000: clodronate taken for two years, women observed for seven years). Oral pamidronate 300 mg a day was evaluated by one study (Van-Holten 1996).

Bone metastases

The incidence of bone metastases did not differ significantly between the bisphosphonate and placebo groups (RR 0.96, 95% CI 0.65 to 1.43; P = 0.86, 3 studies; Analysis 2.1; moderate-quality evidence). In total, there were 76 events in 330 women randomised (Figure 8).

Figure 8. Forest plot of comparison: 2 Advanced breast cancer (ABC), outcome: 2.1 Incidence of bone metastases in ABC (Stage III/IV)



Skeletal-related event (SRE) rate

Kanis 1996 reported a 36% reduction in the SRE rate (P < 0.01, 133 women; Table 4) in the clodronate group compared to placebo group.

Median time to a skeletal-related event (SRE)

Mardiak 2000 reported a trend towards an extended period of time without a SRE when women were taking clodronate (median time: 28.4 months) compared to placebo (median time: 13.4 months) but this difference was not statistically significant (P = 0.42, 73 women; Table 5; low-quality evidence).

Overall survival

Bisphosphonates did not alter survival in women with ABC (RR 0.89, 95% CI 0.73 to 1.09; P = 0.28, 3 studies, 330 women; Analysis 2.2; high-quality evidence). There were 172 deaths in total. Mardiak 2000 and Van-Holten 1996 reported no significant difference in median survival time between bisphosphonate and placebo groups (Table 6).

Quality of life

One study, Van-Holten 1996, asked women to complete a questionnaire (i.e. using a 4-point scale) and concluded that there was no difference in quality of life scores between oral pamidronate or placebo groups (Table 7; moderate-quality evidence).

Adverse, drug-related events or toxicity

The three studies reported very little information (Table 8; Table 9). Of the adverse events reported, bone pain appeared to be similar in both groups (Kanis 1996; Van-Holten 1996). Fatigue was reported to be worse in the pamidronate group than placebo group in one study (Van-Holten 1996).

Metastatic breast cancer and bone metastases (BCBM)

There were 24 studies referring to 25 treatment comparisons: 14 studies compared bisphosphonates to placebo/no bisphosphonates, four studies compared directly different types of bisphosphonates, three studies tested denosumab against intravenous bisphosphonate and four studies tested standard versus reduced frequency of bisphosphonate or denosumab. Of the 14 studies that compared bisphosphonates to placebo/no bisphosphonate, bisphosphonates were administered intravenously in six studies and orally in eight studies. The four studies that compared different bisphosphonates included intravenous pamidronate versus intravenous clodronate or oral clodronate (three-armed studies: Diel 1999; von Au 2016), intravenous zoledronate versus intravenous pamidronate (Rosen 2004) or intravenous zoledronate versus oral ibandronate (ZICE 2014). One study that compared standard versus reduced frequency of bisphosphonate (CALGB-70604 2015) reported data mostly for all cancers rather than specifically for breast cancer.

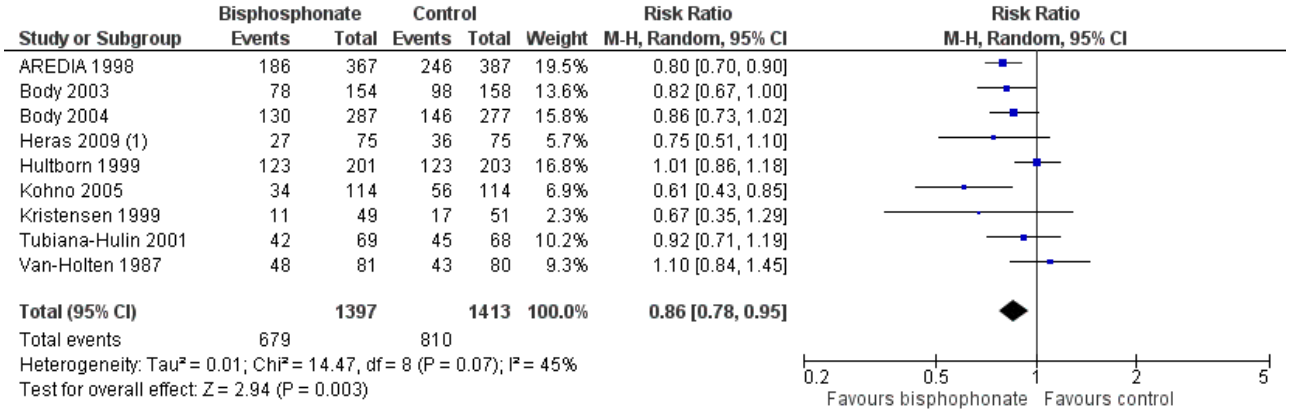
Proportion of participants with skeletal-related events (SREs)

Bisphosphonate versus placebo/no bisphosphonate

Eight out of 14 studies reported the risk of developing a SRE (including hypercalcaemia). Bisphosphonates reduced the risk of an SRE compared with placebo/no bisphosphonate by 15% (RR 0.85; 95% CI 0.77 to 0.95; P = 0.003; Analysis 3.1). There were 1371 SRE events in 2193 randomised women with BCBM. There was significant heterogeneity (I^2 = 56%; P = 0.02). The heterogeneity was largely contributed by Conte 1996 and Hultborn 1999 as both studies assigned a relatively low dose of pamidronate in the treatment arm; 45 mg in Conte 1996 and 60 mg in Hultborn 1999. By removing these two studies in a sensitivity analysis, there was minimal heterogeneity in the remaining six studies (I^2 = 9%; P = 0.36) and the RR was 0.80 (95% CI 0.73 to 0.87; forest plot not shown).

Nine studies reported the risk of developing a SRE (excluding hypercalcaemia). Bisphosphonates reduced the risk of developing a SRE compared with placebo/no bisphosphonate by 14% (RR 0.86; 95% CI 0.78 to 0.95; P = 0.003; Analysis 3.2; Figure 9; high-quality evidence). There were 1489 SRE events in 2810 randomised women. There was no significant heterogeneity (I^2 = 45%; P = 0.07). Examining the funnel plots, it appeared that there was a paucity of negative trials with a high standard error (SE). This suggested that despite our best attempt to search for all relevant studies that examined bisphosphonate versus placebo in this setting, there may be a publication bias due to the absence of smaller negative studies.

Figure 9. Forest plot of comparison: 1 Breast cancer and Bone Metastases (BCBM), outcome: 1.2 Overall risk of SREs in BCBM: bisphosphonate versus control (excluding hypercalcaemia).



Footnotes
(1) Number of participants in each arm was not reported; 50% assumed to be in ibandronate arm and 50% in control arm

Intravenous bisphosphonate versus placebo/no bisphosphonate

Data were available from all six studies. The overall risk of developing a SRE was reduced by 17% in the intravenous bisphosphonates group compared to placebo/no bisphosphonate (RR 0.83; 95% CI 0.73 to 0.95; P = 0.006; Analysis 3.3: Analysis 3.3.1). There were 1251 SRE events in 2072 randomised women. There was significant heterogeneity (I^2 = 69%; P = 0.006), owing to the low-dose pamidronate studies by Conte 1996 and Hultborn 1999. Apart from the three pamidronate studies (AREDIA 1998; Conte 1996; Hultborn 1999) using differing doses of pamidronate, other reasons for the observed heterogeneity may include between-study differences in the duration of bisphosphonate treatment, participant- and disease-related differences in the study populations such as timing of treatment in the women's natural history, the extent of bone metastases and the concomitant anti-cancer treatments used in the studies. The 90 mg pamidronate dose was the registered dose for use in most parts of the world. Therefore, we used the AREDIA 1998 study alone for the analysis of individual bisphosphonates in Analysis 3.4.

Intravenous zoledronate versus placebo

Based on one study, intravenous zoledronic acid (4 mg) reduced the risk of developing a SRE by 41% (RR 0.59; 95% CI 0.43 to 0.82; P = 0.002; 228 participants; Analysis 3.4).

Intravenous pamidronate versus placebo

Based on one study using 90 mg pamidronate, there was a reduced risk of developing a SRE (RR 0.78, 95% CI 0.69 to 0.88; P < 0.0001; 754 participants; Analysis 3.4).

Intravenous ibandronate versus placebo

In two studies, intravenous ibandronate (6 mg) reduced the risk of developing a SRE by 20% (RR 0.80; 95% CI 0.67 to 0.96; P = 0.01; 462 participants; Analysis 3.4). There was no heterogeneity.

Oral bisphosphonate versus placebo/no bisphosphonate

Data were available from five out of the eight studies. Overall, oral bisphosphonates reduced the risk of SREs by 16% compared to placebo/no bisphosphonate (RR 0.84, 95% CI 0.76 to 0.93; P = 0.0007; Analysis 3.3: Analysis 1.3.2). There was no heterogeneity. In total, there were 639 SRE events in 1147 women randomised.

Oral clodronate versus placebo/no bisphosphonate

In the three studies using oral clodronate (1600 mg), clodronate appeared to reduce the risk of developing an SRE by 18% (RR 0.82, 95% CI 0.71 to 0.96; P = 0.01; 422 participants; Analysis 3.4) and there was no heterogeneity.

Oral ibandronate versus placebo

Based on one study, developing an SRE did not differ between oral ibandronate (50 mg) and placebo (RR 0.86, 95% CI 0.73 to 1.02; P = 0.09; 564 participants; Analysis 3.4).

Oral pamidronate versus no bisphosphonate

Based on one study, there was no significant difference in the risk of development a SRE between oral pamidronate (300 mg a day) and no bisphosphonate (RR 0.86, 95% CI 0.70 to 1.05; P = 0.14; 161 participants; Analysis 3.4).

Due to the difference in treatment populations between studies (in terms of participant characteristics, tumour characteristics and other treatments), we avoided direct comparisons of the RR reduction between each bisphosphonate.

Direct comparisons of different bisphosphonate regimens

ZICE 2014 compared oral ibandronate (50 mg daily) and intravenous zoledronate (4 mg every three to four weeks over 96 weeks) in a non-inferiority trial and involved 1404 randomised women. Annual rates of SREs were 0.499 (95% CI 0.454 to 0.549) with ibandronate and 0.435 (95% CI 0.393 to 0.480) with zoledronate. The rate ratio for SREs was 1.148 (95% CI 0.967 to 1.362), the upper CI exceeded the pre-defined margin of non-inferiority of 1.08.

Rosen 2004, a three-arm study, compared intravenous zoledronate (4 mg or 8 mg) and intravenous pamidronate (90 mg) (every three to four weeks for 24 months) using a non-inferiority design and involved 1130 women with breast cancer. In the analysis comparing intravenous zoledronate (4 mg) and pamidronate (90 mg), there was no difference in the proportion of women developing a SRE (excluding hypercalcaemia): 46% (zoledronate (4 mg)) and 49% (pamidronate (90 mg). There was no significant difference seen in the time to first SRE or skeletal morbidity rate (events per year). Within the lytic metastases subgroup in the study (47% of participants), zoledronate produced a significant prolongation of time to first SRE (310 versus 174 days; P = 0.013), a significant reduction in skeletal morbidity rate (1.2 versus 2.4 events; P = 0.008) and a significant reduction in the SRE rate of 30% (P = 0.010).

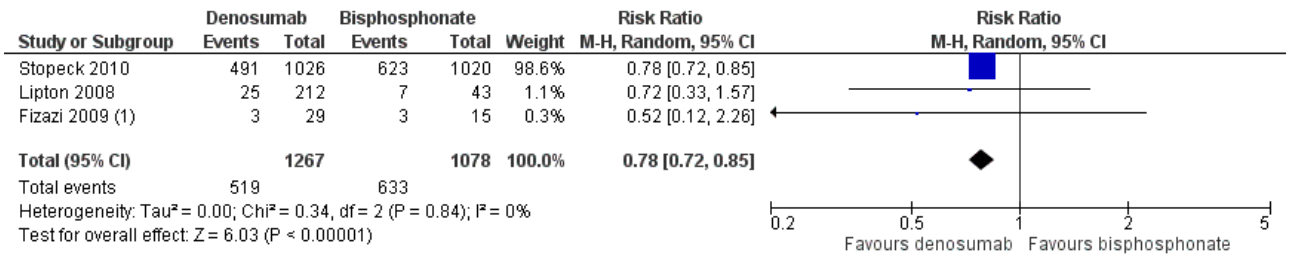
Diel 1999, a three-arm study, compared intravenous pamidronate (60 mg) and clodronate (oral 2400 mg and intravenous 900 mg). At interim analysis, fewer women were reported to have vertebral fractures with oral clodronate (2400 mg; 11 out of 112) than with intravenous clodronate (900 mg; 25 out of 103) or intravenous pamidronate (60 mg; 26 out of 103). However, Diel 1999 has not been published in full and the endpoint of fracture rate was not the same as the SRE, therefore we have not included the results from this study.

von Au 2016, a three-arm study, compared intravenous pamidronate (60 mg) and clodronate (oral 2400 mg and intravenous 900 mg). The secondary endpoint, pathologic fractures, indicated a trend to increased pathologic fractures with oral clodronate (18%; 19 out of 107 women) compared to intravenous pamidronate (7%; 8 out of 109 women) or intravenous clodronate (14%; 8 out of 105 women).

Denosumab versus bisphosphonate

Three RCTs compared denosumab with zoledronate in women with BCBM (Fizazi 2009 (denosumab 180 mg every four weeks versus intravenous bisphosphonate); Lipton 2008; Stopeck 2010) and included 2345 women with advanced BCBM. Denosumab reduced the risk of developing a SRE compared with bisphosphonates by 22% (RR 0.78; 95% CI 0.72 to 0.85; P < 0.00001; Analysis 3.5; Figure 10). There was no heterogeneity. Both Fizazi 2009 and Lipton 2008 compared a range of denosumab regimens to the clinician's choice of bisphosphonate. Fizazi 2009 was a second-line study that enrolled patients with breast cancer, prostate cancer and multiple myeloma after unsuccessful treatment with bisphosphonates. Separate outcomes for the breast cancer subgroup (40% of the treatment population; 46 women) were kindly made available by the study sponsors upon enquiry.

Figure 10. Forest plot of comparison: 1 Breast cancer with bone metastases (BCBM), outcome: 1.3 Overall risk of skeletal events in BCBM: denosumab versus bisphosphonate



Footnotes
(1) 25 weeks of follow-up (data provided by Amgen pharmaceutical)

Standard versus reduced frequency bisphosphonate/bone agent

Three RCTs (Fizazi 2009; OPTIMIZE-2 2014; ZOOM 2013), examined standard versus reduced frequency of bisphosphonates/bone agents on the risk of developing SREs and there appeared to be no significant difference in risk (RR 0.96, 95% CI 0.72 to 1.26; P = 0.75; Analysis 3.6). There were 161 events in 901 randomised women, and no heterogeneity. In ZOOM 2013, the primary outcome was SRE morbidity rate (SRE per patient per year). The reduced-frequency bisphosphonate group (every 12 weeks) had a SRE morbidity rate of 0.26 (95% CI 0.15 to 0.37) compared to the standard-frequency group of 0.22 (95% 0.14 to 0.29). The between-group difference was 0.04 and the upper limit of one-tailed 97.5% CI was 0.17, within the pre-specified non-inferiority margin (0.19). The data should be interpreted with caution as the study was hampered by a

lower event rate than anticipated and potentially under-powered; the short, 12-month follow-up may be inadequate to capture cumulative differences in efficacy and a rise in bone-turnover markers among the reduced-frequency group. An additional study, CALGB-70604 2015, reported the proportion of participants in each group who had more than one SRE. In participants with breast cancer (820 out of 1822 participants), there were 113 SREs in those women receiving zoledronate intravenously every four weeks and 119 SREs in those receiving zoledronate every 12 weeks (P = 0.43). The denominators were not reported in the abstract so these data could not be included in Analysis 3.6.

Skeletal-related event rate

The overall SRE rate was reported in 16 of the 25 treatment comparisons (Table 10). We did not include data from Martoni 1991 because follow-up imaging was incomplete for many participants. SREs were reported differently across studies and the data were summarised rather than formally combined.

The SRE rate was lower with bisphosphonates compared to placebo in 10 studies (median reduction of 28%; range from 14% to 48%), with statistically significant reductions reported in eight studies. In Rosen 2004, the skeletal morbidity rate (events per year, excluding hypercalcaemia) for the 4 mg zoledronate arm was 0.9 compared with 1.49 for the 90 mg pamidronate arm (P = 0.125). Multiple-event analysis, using the method of Andersen-Gill (Andersen 1982), was reported to show a reduction in the risk of developing any skeletal complication (including hypercalcaemia) by 20% (zoledronate (4 mg) compared with pamidronate (90 mg), RR = 0.80, 95% CI 0.66 to 0.97; P = 0.025), suggesting a possible advantage of zoledronate (4 mg) compared with pamidronate (90 mg). In Stopeck 2010, denosumab was superior to zoledronate in reducing the mean skeletal morbidity rate (RR 0.78, denosumab: 0.45 events; zoledronate: 0.58 events per participant per year; P = 0.004). This study defined the mean skeletal morbidity rate as "the ratio of the number of SREs per patient divided by the patient's time at risk".

Overall, the results were largely concordant with the findings in the analysis of the proportion of women with SREs (Analysis 3.2).

Median time to skeletal-related event

Data were available from 14 out of 25 treatment comparisons. All results are presented in Table 11.

Twelve studies compared bisphosphonates to placebo. Bisphosphonates delayed the median time to an SRE with a median ratio of 1.43 (95% CI 1.29 to 1.58; P = < 0.00001, 9 studies, 2891 participants, no heterogeneity; Analysis 3.7). Three of the 12 studies did not report sufficient data to calculate the median time to an SRE (i.e. no P value reported or an SRE was not reached) but two of these three studies reported results in favour of bisphosphonates. Further details are presented in Table 11. In general, in 11 out of 12 studies, the median time to an SRE in the bisphosphonates group ranged from 8.7 months to 20.8 months and in the placebo group ranged from 4.9 months to 14.9 months. Three studies of intravenous pamidronate showed significant delays in the median time to a SRE compared with placebo/no bisphosphonate (AREDIA 1998; Conte 1996; Hultborn 1999). Event-free survival was also reported to be longer with intravenous ibandronate (6 mg) than with placebo (Body 2003, T/C (treatment/control) 1.34; P = 0.018; Heras 2009, T/C 1.50; P = 0.007). Three studies of oral clodronate reported a statistically significant delay in the time to a SRE (Kristensen 1999; Paterson 1993; Tubiana-Hulin 2001). One study of intravenous zoledronate demonstrated significant improvement in median time to a SRE (Kohno 2005). Overall, we rated the quality of evidence as high.

One study, Rosen 2004, reported no significant difference in the time to a SRE between intravenous zoledronate and intravenous pamidronate in the overall breast cancer study population in the single comparison study (Rosen 2004). However, as described previously, in the subgroup of participants with lytic-only metastases, 4 mg zoledronate significantly prolonged the median time to the first SRE compared with 90 mg pamidronate (median, 310 days versus 174 days respectively; P = 0.013; Rosen 2004). Similarly, in the breast-cancer subgroup treated with hormonal therapy, 4 mg zoledronate significantly prolonged the median time to the first SRE compared with 90 mg pamidronate (median, 415 days versus 370 days respectively; P = 0.047).

One study reported that denosumab significantly improved median time to a SRE compared to zoledronate (Stopeck 2010).

Overall survival

Bisphosphonate versus placebo/no bisphosphonate

Data were available from seven out of the 14 studies comparing bisphosphonates and placebo/no bisphosphonate. Overall, there was no significant difference in overall survival between two groups (RR 1.01; 95% CI 0.91 to 1.11; P = 0.85; Analysis 3.8; with some heterogeneity: I^2 = 49%, P = 0.07; moderate-quality evidence). There were 1111 deaths in 1935 randomised women.

Direct comparisons of different bisphosphonate regimens

Data from studies directly comparing different bisphosphonates were sparse with only one out of four studies reporting overall survival (ZICE 2014). ZICE 2014 compared oral ibandronate 50 mg and intravenous zoledronate 4 mg, and observed no significant difference in survival between the groups (HR 1.086, 95% CI 0.948 to 1.245, P = 0.24). There were 831 deaths in 1401 randomised women.

Denosumab versus bisphosphonate

Only one study (Stopeck 2010) out of three studies comparing denosumab to a bisphosphonate reported overall survival. Stopeck 2010 observed no difference in survival between denosumab and zoledronate (P = 0.49; Table 12).

Standard versus reduced frequency bisphosphonate/bone agent

For the two studies comparing standard versus reduced frequency bisphosphonate/denosumab, overall survival was not reported in either study. A summary of studies reporting median survival time for each study is provided in Table 12.

Bone pain

Eleven out of 14 studies tested the effects of bisphosphonates (compared with placebo or no bisphosphonate) on bone pain while all studies examining direct comparisons of different bisphosphonates or denosumab compared to bisphosphonates reported on bone pain (see Table 13; moderate-quality evidence). Only one study reported the frequency of bone pain when comparing standard versus reduced therapy (ZOOM 2013). Various pain assessment tools were used across studies, ranging from the

4-point visual analogue scales to referenced pain scales (e.g. Brief Pain Inventory).

For those studies comparing a bisphosphonate to placebo, there were significant differences in pain in one study of intravenous pamidronate (90 mg) (AREDIA 1998), one study of intravenous ibandronate (6 mg) (Body 2003), one study of intravenous zoledronate (Kohno 2005), one study of oral clodronate (Tubiana-Hulin 2001), one study of oral pamidronate (Van-Holten 1987) and the pooled studies of 50 mg oral ibandronate (Body 2004). The two lower-dose pamidronate studies (Conte 1996; Hultborn 1999), one study of oral ibandronate (Tripathy 2004) and two clodronate studies (Kristensen 1999; Martoni 1991) reported no significant difference in bone pain between bisphosphonate and placebo/no bisphosphonate.

Four bisphosphonate comparison trials studied relative benefits of ibandronate, pamidronate, clodronate, zoledronate and denosumab on bone pain. In Diel 1999, better pain reduction was reported with the use of intravenous bisphosphonates (clodronate or pamidronate) than with oral clodronate, however the final report of this study has not yet been published. In von Au 2016, no significant differences in pain scores were noted among the groups (intravenous pamidronate versus intravenous or oral clodronate). In Rosen 2004, no difference in overall pain was observed between intravenous zoledronate or intravenous pamidronate compared with baseline. ZICE 2014 reported no difference in bone pain between intravenous zoledronate and oral ibandronate.

For the comparison of denosumab and bisphosphonate, Stopeck 2010 reported prolonged median time to develop moderate/severe pain for participants with no pain at baseline (denosumab versus zoledronate: HR 0.78; P = 0.0024) and had a lower proportion of participants who had no pain at baseline, and had moderate/severe pain at week 73 (denosumab 14.8% versus zoledronate 26.7%). The median time to pain improvement was similar between treatment arms (denosumab 82 days versus zoledronate 85 days: HR 1.02; P = 0.72). Neither Fizazi 2009 nor Lipton 2008 collected data using pain assessment tools.

For the comparison of standard versus reduced bisphosphonate, ZOOM 2013 reported no significant difference in bone pain. OPTIMIZE-2 2014 reported preliminary data in the clinical trial record where the change from baseline in the mean composite Brief Pain Inventory score was 0.24 in the standard bisphosphonate group and 0.31 in the reduced bisphosphonate group. We await statistical analysis.

Quality of life

Eight out of the 25 treatment comparisons provided quality-of-life information (Table 14; moderate-quality evidence). Five studies tested the effect of bisphosphonates compared with placebo on participant-rated quality of life using a validated quality-of-life scale (Spitzer Quality of Life Index: AREDIA 1998, EORTC QLQ-C30: Body 2003, Body 2004, Kristensen 1999, validated 4-point ordinal scale: Van-Holten 1987). Overall, global quality-of-life scores decreased to a lesser extent in participants receiving intravenous ibandronate 6 mg (Body 2003), oral ibandronate 50 mg (Body 2004) and intravenous pamidronate 90 mg (AREDIA 1998) compared to placebo. There was no significant change in overall quality of life between clodronate oral 800 mg twice a day compared to no bisphosphonate (Kristensen 1999).

Two studies comparing different bisphosphonate regimens reported no significant difference between groups in quality-of-life scores using the FACT-G or EORTC QLQ-30 (Rosen 2004: intravenous zoledronate 4 mg or 8 mg versus intravenous pamidronate 90 mg; ZICE 2014: oral ibandronate 50 mg versus zoledronate 4 mg). One study that compared a bone-targeted agent to bisphosphonate reported that participants in the denosumab group had a clinically meaningful improvement in quality of life (on FACT-G) compared to zoledronate (Stopeck 2010). Quality of life was not collected and reported in the four studies comparing standard versus reduced bisphosphonate/bone agent (CALGB-70604 2015; Fizazi 2009; OPTIMIZE-2 2014; ZOOM 2013).

Adverse, drug-related events or toxicity

Osteonecrosis of the jaw (ONJ)

Six studies reported ONJ (Heras 2009; Lipton 2008; OPTIMIZE-2 2014; Stopeck 2010; ZICE 2014; ZOOM 2013) with no reported differences between groups (Table 15).

Hypocalcaemia

Of the 10 studies that reported hypocalcaemia, four studies reported an increased incidence of hypocalcaemia when administering oral ibandronate (Body 2004), intravenous, low-dose pamidronate (Conte 1996), intravenous zoledronate (Kohno 2005; grade I hypocalcaemia) and oral-clodronate groups (Kristensen 1999) compared to placebo/open. Denosumab (every 4 or 8 weeks) had a higher incidence of hypocalcaemia compared to clinician's choice of intravenous bisphosphonate or intravenous zoledronate (two studies: Fizazi 2009; Stopeck 2010; Table 15). There was no difference in hypocalcaemia in the one study comparing standard to reduced-frequency zoledronate (OPTIMIZE-2 2014).

Renal dysfunction

Fourteen studies reported on renal dysfunction and most of the studies did not observe significant differences between treatment and comparator groups except for Rosen 2004, where renal toxicity was greater in the intravenous-zoledronate than intravenous-pamidronate arm, Stopeck 2010, where renal toxicity occurred more frequently in the intravenous-zoledronate group than denosumab group (Table 15). We compared grade 3/4 renal toxicity events between treatment and comparator groups where reported (Table 15).

Drug-related death

In the nine studies that collected data on treatment-related deaths, no differences were observed between groups (Table 15).

Nausea

Eleven studies reported nausea and none observed substantial differences between the groups (Table 16).

Gastrointestinal events

In the 11 studies reporting gastrointestinal toxicity, there were no significant differences observed except in three studies (Table 16). In Kohno 2005, abdominal pain was higher in the intravenous-zoledronate group than placebo; in Van-Holten 1987, gastrointestinal toxicity was the cause of withdrawal in 20 (25%) participants treated with oral pamidronate and in ZOOM 2013, the incidence of gastrointestinal events was significantly higher in the

intravenous-zoledronate, 4-week group (42%) than 12-week group (31%).

Fatigue

Of the 10 studies that reported fatigue, there were no significant differences between treatment and comparator groups except in two studies (Table 16). In AREDIA 1998, there was an increase in fatigue in the intravenous-pamidronate 90 mg versus placebo group and the same was observed in the intravenous-zoledronate 4 mg group compared to placebo in Kohno 2005.

Fever

Of the nine studies that reported fever, two studies observed an increase in fever in the bisphosphonate arm compared to placebo (AREDIA 1998: pamidronate 90 mg intravenous versus placebo; Kohno 2005: zoledronate 4 mg intravenous versus placebo) and one study had an increase in the incidence of fever in the intravenous-bisphosphonates group compared to denosumab (every 4 or 12 weeks) (Stopeck 2010). We compared grade 3/4 fever or influenza-type events between treatment and comparator groups where reported (Table 16).

Sensitivity analysis: including poor-quality trials in BCBM analysis

We included two studies with poor overall quality ratings in the overall review (Elomaa 1983; Martoni 1991). We did not include the data from these two studies in the primary analysis of the proportion of participants developing SREs because of unclear or unreported data. When we included the Martoni 1991 study (6 events, 18 participants), the RR for developing a SRE changed negligibly. Similarly, when we included data from the Elomaa 1983 study (19 events, 34 participants) in overall survival analysis, there was a negligible change in the risk of death. The inclusion or exclusion of either study did not affect the conclusions of this review.

DISCUSSION

Summary of main results

Early breast cancer

This review update provides moderate- to high-quality evidence that the use of bisphosphonates as part of the treatment plan for women with early breast cancer provides a beneficial effect in reducing the incidence of bone metastases compared to placebo or observation. Most of these studies used either intravenous zoledronate (4 mg every three to six months for one to five years) or oral clodronate (1600 mg daily for two to three years). As expected, there appeared to be no reduction in the incidence of visceral metastases, locoregional recurrence, recurrence (defined as locoregional plus distant recurrence) or fractures with bisphosphonates compared to placebo or observation. However, the confidence intervals were wide in some cases (for example, fracture incidence) suggesting that studies may not be adequately powered for these endpoints. Similarly, in the three recent studies comparing immediate versus delayed bisphosphonate administration, there did not appear to be a significant effect of immediate or delayed bisphosphonates on the incidence of bone metastases, and this lack of an effect was evident when assessing visceral metastases, locoregional recurrence and recurrence.

In this review update, we introduced a new analysis of overall survival using time-to-event data, as this approach is considered to be a more appropriate method rather than using dichotomous data (Tierney 2007). By analysing published and unpublished aggregate data, there was an overall survival benefit in women with early breast cancer receiving bisphosphonates treatment (based on nine studies involving 13,949 women). The bisphosphonates administered were mainly intravenous zoledronate or oral clodronate (four studies each). There was significant heterogeneity, which appears to be due to different effects based upon menopausal status. The group as a whole had significant heterogeneity for the overall survival and disease-free survival outcomes. This heterogeneity was removed when assessed by menopausal status.

Bisphosphonates were found to provide a significant benefit for overall survival in postmenopausal women only. This analysis was based on four studies involving 6048 women who received either intravenous zoledronate (including immediate zoledronate) or oral clodronate. This beneficial effect was not observed in premenopausal women (two studies, 3501 women). The finding was replicated in the analysis of disease-free survival that suggested bisphosphonates improved disease-free survival in postmenopausal women and not premenopausal women (postmenopausal studies: seven studies, 8314 women; premenopausal studies: four studies, 5493 women).

Whilst this benefit is based on a subgroup analysis of these trials, the data are suggestive of a differential effect of treatment based on menopausal status since heterogeneity was removed. There are ongoing trials testing this hypothesis and, once completed, these trials will provided robust evidence of whether bisphosphonates improve survival for menopausal women.

Adjuvant denosumab reduced the incidence of fractures compared to placebo (based on one study) and data for mature overall survival and disease-free survival are awaited. None of the studies reported quality-of-life measures.

Advanced breast cancer without bone metastases

As per the original review, the evidence was based on three studies published in 1996 and 2000. Oral bisphosphonates (either clodronate 1600 mg a day for two to three years or pamidronate 300 mg a day) in women with advanced disease, without clinically evident bone metastases, did not appear to have an effect on the incidence of skeletal metastases compared to placebo, and did not provide a survival benefit. However, the confidence intervals were very wide and only three studies involving 330 women were included. Only one study collected and reported the incidence of SREs with a 36% reduction in events in women receiving oral clodronate compared to placebo. One study reported quality of life and there was no apparent difference in quality-of-life scores between oral pamidronate and placebo.

Metastatic breast cancer and bone metastases

Overall, bisphosphonates (intravenous or oral) reduced the incidence of SREs and rate of SREs when compared to placebo/observation. Intravenous and oral bisphosphonate reduced the risk of a SRE by 17% and 16%, respectively. The studies treating intravenously used a wide range of bisphosphonates: zoledronate 4 mg (one study), pamidronate 45 mg to 90 mg (three studies) and ibandronate 6 mg (two studies), while oral bisphosphonates

included clodronate 1600 mg a day (three studies), ibandronate 50 mg (one study) or pamidronate 300 mg (one study). Similarly, there was reduced risk of SREs (by 22%) in women receiving denosumab (range: 30 mg, 120 mg or 180 mg subcutaneous every 4 weeks) compared to intravenous bisphosphonate. There was at least equivalent efficacy (or no worse) in the incidence of SREs when different bisphosphonate regimens were compared (e.g. intravenous zoledronate versus intravenous pamidronate) or when standard versus delayed frequency of bisphosphonates was tested. The only exception was that oral ibandronate appeared inferior to intravenous zoledronate (ZICE 2014). The median time to a SRE was significantly longer in the bisphosphonates group than placebo/observation.

In this review update, half of the studies reported survival data for the comparison of bisphosphonate versus placebo. Of these, there was no evidence of an effect of bisphosphonates on survival. Only one study testing the effects of denosumab reported on overall survival and this study reported no significant effect of denosumab when compared to bisphosphonate. None of the studies on standard versus delayed frequency of bisphosphonates collected or reported overall survival data.

In the majority of cases, quality-of-life measures were better with bisphosphonates than with placebo. A similar trend was observed with women receiving denosumab than bisphosphonates. None of the studies on standard versus delayed frequency of bisphosphonates collected or reported quality-of-life data.

Toxicity

Following a thorough review of toxicity, adverse events for bisphosphonates or denosumab of any grade were generally uncommon, and grade 3/4 adverse events were rare but did include impaired renal function and osteonecrosis of the jaw. Bisphosphonates carried a small excess risk of acute-phase reactions (such as fever, fatigue and nausea) but these were mostly grade 1 or 2, or the toxicity grade was unspecified.

Overall completeness and applicability of evidence

Many second-generation EBC studies that were specifically designed to detect differences in overall survival or disease-free survival between treatment and control arms have completed accrual and are awaiting analysis (Characteristics of ongoing studies). Among the large RCTs that use recurrence as their primary endpoints, there are four zoledronate versus placebo studies (El-Ibrashi 2016; HOBOE 2013; JONIE-1 2013; NEOZOTAC). In addition, SWOG-S0307 2015 is investigating the relative potency between zoledronate, clodronate and oral ibandronate for 36 months; we have contacted the trialists. Denosumab is also pushing forward to be studied in preventing recurrence in EBC studies with two ongoing studies; one closed to recruitment (D-CARE 2011) and the other having commenced recruitment (Kummel 2016 (GeparX)).

The included studies used a range of bisphosphonates and schedules. In the majority of cases, the duration of treatment ranged from two to five years. The variations in bisphosphonate regimens involved: (a) zoledronate: 4 mg every six months for three years (ABCSG-12 2011) or five years (E-ZO-FAST 2012; Z-FAST 2012; ZO-FAST 2013), or 4 mg de-escalating schedule over five years (AZURE 2014); (b) clodronate: oral 1600 mg a day for two to three years (NSABP-34 2012; Powles 2006; Saarto 2004) or (c) pamidronate: oral 300 mg a day for two years (Kristensen 2008).

The immediate commencement of adjuvant bisphosphonates was not superior to a delayed start, triggered by falling BMD or fracture, in preventing recurrence (or any recurrence sub-set) or improving survival. These trials were primarily powered to detect differences in BMD at 12 months and were not powered for clinical outcome data such as recurrence, disease-free survival or overall survival.

The majority of recently published studies examining the effects of bisphosphonates or bone-modifying agents in metastatic breast cancer with bone metastases did not collect or report data on overall survival. The ongoing studies intend to use bone pain or SREs, or both, as the primary endpoints (Characteristics of ongoing studies). Five of these studies will be investigating upfront versus delayed bisphosphonates or denosumab while the others are comparing different bisphosphonates head-to-head (e.g. zoledronate versus pamidronate, denosumab versus zoledronate).

Similar to the EBC studies, the included studies in the BCBM setting used a wide range of bisphosphonate agents and schedules. The duration of treatment ranged from 25 weeks (Fizazi 2009) to three years (Paterson 1993). The optimal timing and duration of treatment for women with BCBM remains uncertain.

Quality of the evidence

In general, we judged the overall body of evidence to be moderate or high quality across the three treatment settings (see: Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3). In the cases where some heterogeneity was observed in the meta-analyses, the heterogeneity could be explained by removing studies that used sub-optimal doses of pamidronate (45 mg or 60 mg) that are rarely used in practice today or by analysing data by menopausal status (as in the case for overall survival in the EBC studies). Therefore in the majority of these cases, we did not downgrade the quality of the evidence. Most of the outcomes presented in the 'Summary of findings' table indicated consistent findings across the studies, and this held true when we carried out additional analyses by considering mode of drug administration (e.g. intravenous bisphosphonate versus placebo; oral bisphosphonate versus placebo).

We downgraded the quality of the evidence primarily in those cases where outcomes (such as bone pain or quality of life) were measured on unvalidated scales or questionnaires and involved participant self-reporting when the participant was aware of the drug received.

Potential biases in the review process

This review has aimed to provide a thorough overview of the benefits and toxicities from bisphosphonates and denosumab across studies and treatment settings. Despite having conducted a comprehensive search of medical databases and key conference proceedings, we may not have identified all potentially relevant studies. We conducted tests for funnel plot asymmetry for main outcomes and the plots did not strongly indicate publication/reporting bias or other sources of bias (e.g. true heterogeneity). In the review update, we contacted study authors if (a) data were not fully reported in the full-text article or (b) overall survival or disease-free survival were not reported by menopausal status. In some cases, data were available in abstract form (e.g. CALGB-70604 2015; Diel 1999; OPTIMIZE-2 2014; SWOG-S0307 2015). Clinical trials registries were also searched and matched against eligible trials

though some ongoing trials in the registries may have been missed due to the large number of trial records retrieved on this topic.

For a number of studies, we are still awaiting more mature follow-up data, particularly in the BCBM studies and a number of studies poorly reported toxicities that in part reflects the age of some of these studies (e.g. from the late 1990s particularly in the ABC studies).

We have indicated throughout the review that a number of large trials are awaiting final completion and publication in EBC and BCBM before firm conclusions can be drawn.

Agreements and disagreements with other studies or reviews

Early breast cancer

The finding of this systematic review replicate the main findings presented in the American Society of Clinical Oncology (ASCO) ASCO Guidelines 2017. The individual participant meta-analysis (IPD) conducted by the Early Breast Cancer Trialists Collaborative Group (EBCTCG 2015) that involved 18,766 women described reductions in overall recurrence (RR 0.94, 95 % CI 0.87 to 1.01; P = 0.08, heterogeneity across trials P = 0.04) and distant recurrence (RR 0.92, 95% CI 0.85 to 0.99; P = 0.03, heterogeneity across trials P = 0.04) but highlighted these to be of modest effect size and/or borderline statistical significance. The EBCTCG 2015 meta-analysis also reported that adjuvant bisphosphonates among premenopausal women had no apparent effect on any outcome; but among 11,767 postmenopausal women it produced highly significant reductions in recurrence (RR 0.86, 95% CI 0.78 to 0.98; P = 0.002), distant recurrence (RR 0.82, 95% CI 0.74 to 0.92, P = 0.0003), bone recurrence (RR 0.72, 95% CI 0.60 to 0.86; P = 0.0002), and breast cancer mortality (RR 0.82, 95% CI 0.73 to 0.93, P = 0.002). In our analyses, we did not detect an effect of bisphosphonates for visceral metastases, overall recurrence (locoregional plus distant recurrence) or locoregional recurrence. However we did observe a benefit from bisphosphonates for bone recurrence and also noted for overall survival (HR 0.91, 95% CI 0.83 to 0.99) and disease-free survival (specifically comparing intravenous zoledronate versus placebo/delayed zoledronate: HR 0.89; 95% CI 0.80 to 0.98; P = 0.02) when analysing data using time-to-event outcomes. We did not collect information specifically on breast cancer-specific mortality. Our aggregate meta-analysis for disease-free survival and overall survival (using time-to-event outcomes) was limited to nine trials for overall survival (13,949 women) and seven trials for disease-free survival (12,578 women) and outcome data stratified by menopausal status were not available for all these studies. In those studies where data were available for postmenopausal women, preliminary evidence suggested a benefit from adjuvant bisphosphonates for overall survival and disease-free survival. These overall survival findings concur with ASCO Guidelines 2017.

Advanced breast cancer without bone metastases

No other publications are on this topic; all new studies are undertaken in women with BCBM.

Breast cancer with bone metastases

The results of the meta-analyses in this review are largely consistent with the ASCO Guidelines 2011 on the use of bisphosphonate treatment in women with BCBM. The guideline recommends the use of intravenous bisphosphonates (pamidronate, zoledronate) in BCBM. ASCO Guidelines 2011 also recommends the use of denosumab and acknowledges the fact that ibandronate and clodronate are used for the management of BCBM in countries other than the USA, but it has not discussed the relevance of these two drugs or included them in its recommendations because these two drugs are not Federal Drug Agency (FDA)-approved in the USA for the indication of BCBM.

Both ASCO Guidelines and European Society for Medical Oncology (ESMO) Guidelines (ESMO Clinical Practice Guidelines 2014) recognise the paucity of evidence of treatment beyond two years. None of the studies included in this Cochrane Review update included data beyond two years.

AUTHORS' CONCLUSIONS

Implications for practice

Early breast cancer

Adjuvant bisphosphonates reduce bone metastases and most of the studies used either intravenous zoledronate or oral clodronate. On the basis of published and unpublished aggregate data available for this meta-analysis, there is evidence to suggest that adjuvant bisphosphonates improve overall survival and there is preliminary evidence indicating an overall survival and disease-free survival benefit is in those women who were postmenopausal when treatment began. Of the studies included in the stratified analysis by menopausal status, studies used either intravenous zoledronate (4 mg), oral clodronate (1600 mg a day) or oral ibandronate (50 mg a day). The results are limited by the fact that these are subgroup analyses of trials rather than trials planned to test whether the effect differs between postmenopausal and premenopausal or perimenopausal women.

Advanced breast cancer without bone metastases

The use of bisphosphonates outside of clinical research is currently not supported by evidence.

Breast cancer with bone metastases

In general, bisphosphonates are effective in reducing the risk of skeletal-related events (SRE), delaying time to SRE, reducing bone pain and improving quality of life. Most of the included studies with data involved intravenous zoledronate or oral clodronate. When comparing different bisphosphonates, one bisphosphonate compared to another did not show any superior benefit, except for one study where ibandronate was inferior to zoledronate in terms of the number of SREs. Denosumab is effective in reducing bone pain and delaying the time to SREs compared to placebo.

In general, when considering all settings, toxicity is generally mild, with rates of osteonecrosis of the jaw (ONJ) across studies in mature data sets approximately less than 0.5%.

The ideal choice of bisphosphonates and other bone agents may be different from woman to woman. It is likely to depend on the bisphosphonate efficacy versus its toxicity, ease of administration, patient's prior treatment, patient preference, drug availability and local guidelines and legislation.

Implications for research

This meta-analysis suggests that adjuvant bisphosphonates provide a survival benefit for postmenopausal women with early breast cancer however further trials are awaited before a firm conclusion can be made. Trials should be stratified and reported by menopausal status at study entry. Multi-variate analysis reporting rates of recurrence within different risk groups (or stage of the breast cancer), menopausal status, high or low oestrogen level and endocrine receptor status will be useful in finding a subgroup that will benefit from bisphosphonates. In addition, a uniform definition of recurrence or invasive recurrence would help when combining data for meta-analysis. The benefit of bisphosphonates in women receiving aromatase inhibitors in early breast cancer or targeted non-cytotoxic therapy, such as treatment with monoclonal antibody to HER2-neu, or both, requires further study.

The following outcomes should be considered for inclusion and reported in future trials of bisphosphonates in early breast cancer.

1. Overall survival
2. Disease-free survival
3. Bone metastases and
4. Toxicity

In women with advanced breast cancer and bone metastases, the questions still remain regarding: (a) the optimum commencement time of bisphosphonate therapy, (b) the duration of treatment and (c) what to do in participants with progressive bone disease and symptoms, despite bisphosphonates and systemic anti-cancer therapy. The uniform and standardised reporting of SRE rates would assist efficacy comparisons between drugs.

The following outcomes should be considered for inclusion and reported in future trials of bisphosphonates in breast cancer and bone metastases.

1. Numbers of participants developing individual SREs in the study period (with hypercalcaemia reported separately)
2. Time to the first SRE
3. Validated, participant-rated measures of bone pain, quality of life and other relevant symptoms
4. Systematic assessment of toxicities, including fever, flare, gastrointestinal symptoms, hypocalcaemia and renal toxicity
5. Measurement of resource use and incorporation of cost-effectiveness analyses
6. The incidence of ONJ.

Finally, trial authors should consider reporting effect sizes such as the hazard ratio and its confidence interval for survival outcomes, in line with the CONSORT statement.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

ABCSG-12 2011

Methods	Adjuvant zoledronic acid study. Open-label, randomised, placebo-controlled phase III trial
Participants	N = 1803 women Premenopausal women with stage I/II hormone-positive BC, ≤ 10 axillary lymph nodes. All women on ovarian suppression with monthly goserelin. Exclusion criteria included T1a, T4d tumours and pre-operative radiotherapy. Pre-operative chemotherapy was allowed but no patients received adjuvant chemotherapy. Post-operative radiotherapy was administered according to guidelines from local institutions. Baseline characteristics: similar between groups. Median age (45 years in both arms); > stage II (21.7% zoledronic acid, 21.2% no zoledronic acid), node-positive (30.4% zoledronic acid, 30.4% no zoledronic acid); no women on adjuvant chemotherapy
Interventions	2 x 2 factorial design (randomised 1:1:1:1) Goserelin (3.6 mg monthly) plus either tamoxifen (20 mg daily) or anastrozole (1 mg daily) With or without zoledronic acid 4 mg every 6 months (protocol amended late 2000 from 8 mg to 4 mg every 6 months)
Outcomes	Primary endpoint: DFS (local or regional recurrence, cancer in contralateral breast, distant metastasis, second primary carcinoma, or death from any cause) Secondary endpoints: RFS, OS, measures of BMD Exploratory endpoint: BMFS, safety
Notes	Statistics: powered to detect a HR of 1.8 with 90% power and 95% confidence between tamoxifen and anastrozole. ITT analysis. Final efficacy analysis at median 62 months' follow-up (ABCSG-12 2011)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated adaptive randomisation method"
Allocation concealment (selection bias)	Low risk	"Assign treatment groups via an automated telephone service"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	In this open-label trial, no investigators, staff at participating centres, or participants were masked to treatment group; however, individuals analysing disease recurrence from laboratory results were masked to treatment group. All events underwent double central medical review with masked source data, and only histopathology reports or appropriate imaging were regarded as acceptable for confirmation of disease recurrence
Incomplete outcome data (attrition bias)	Low risk	ITT analysis. No missing outcome data

ABCSG-12 2011 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported
Other bias	Low risk	Study appeared to be free of other sources of bias

ABCSG-18 2015

Methods	Multi-centre, phase III, prospective, randomised, double-blind, parallel assignment. Accrual from Dec 2006 to July 2013, 58 centres Austria/Sweden
Participants	N = 3420 women Post-menopausal women ≥ 45 years with EBC; ER and/or PgR positive; currently on or will commence non-steroidal aromatase inhibitor (anastrozole, letrozole) Baseline characteristics: similar between groups. Mean tumour size: 3.81 cm zoledronic acid group; 3.56 cm control group Node-positive disease in 38% zoledronic acid group and 33% control group respectively. HER2-positive disease in 13% zoledronic acid group and 10% control group respectively
Interventions	Denosumab 60 mg (n = 1711) or placebo (n = 1709) subcutaneously every 6 months. Other treatment: all women received 4 cycles of neoadjuvant epirubicin (75 mg/m^2) and docetaxel (75 mg/m^2) every 3 weeks with G-CSF, followed by surgery and 2 cycles of adjuvant epirubicin plus docetaxel. Adjuvant radiotherapy, endocrine therapy or trastuzumab as indicated. 5-year follow-up
Outcomes	Primary endpoint: time to first clinical fracture Secondary endpoints: incidence of new fractures, BMD changes, DFS, BMFS, OS
Notes	clinicaltrials.gov/ct2/show/NCT00556374 The primary endpoint was time from randomisation to first clinical fracture, analysed by ITT

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomly permuted block design with block sizes 2 and 4, stratified by type of hospital regarding Hologic device for DXA scans, previous aromatase inhibitor use, and baseline bone mineral density"
Allocation concealment (selection bias)	Low risk	"assigned by an interactive voice response system"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Patients, treating physicians, investigators, data managers, and all study personnel were masked to treatment allocation."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Clinical follow-up, including fracture assessment and other diagnostic restaging procedures when indicated, was done at least every 6 months until the primary analysis data cutoff date on March 26, 2014, and annually thereafter. Patients remained on trial medication until up to 6 months after the primary analysis data cutoff date was reached. The assessments of the patients and

ABCSG-18 2015 *(Continued)*

		the recording of adverse events followed the protocol-defined regular schedule"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Good compliance, low numbers lost to follow-up and ITT analysis Denosumab: 95% (per protocol N = 1636/ ITT N = 1711) Placebo: 96% (per protocol N = 1646 / ITT N = 1709) DFS and OS data immature, follow-up ongoing
Selective reporting (reporting bias)	Low risk	All pre-specified endpoints were addressed
Other bias	Low risk	Study appeared to be free of other sources of bias

Aft 2012

Methods	(Neo)adjuvant zoledronic acid study. Randomised, open-label trial. Patients from Siteman Cancer Center, USA (2003-2006)
Participants	N = 120 Stage II-III (> T2 and/or N1) newly diagnosed BC, ECOG 0-1, with no evidence of distant metastases
Interventions	4 mg zoledronate every 3 weeks for 1 year (commencing with first dose of chemotherapy) or open-label control
Outcomes	Primary endpoint: DTC in bone marrow at baseline and 3 months. DTCs were measured by bone marrow collection from each anterior iliac crest. It was defined as anti-pan-cytokeratin (CK) antibody-positive, morphologically consistent cells as viewed by two independent pathologists Secondary endpoints: bone-turnover markers, measured at baseline, 3 months and 12 months; BMD, measured at baseline and 12 months
Notes	Statistics: the study was designed with > 80% power and 0.05 significance level to detect a 20% to 26% difference in DTCs at baseline compared to 3 months Both DFS and OS categorical event data not published and cannot be extracted from either 2-year (Aft 2010) or 5-year (Aft 2012) follow-up publications. Study authors contacted to provide data. Trialists kindly provided unpublished trial data to the Cochrane Review team.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomisation by formal probability model and implemented with SAS process plan generated by statistician
Allocation concealment (selection bias)	Low risk	Allocation placed in sequentially numbered, opaque envelopes in locked cabinet, only accessible to study's patient co-ordinator after enrolment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label thus no blinding to participant

Aft 2012 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"the interpreting pathologists were masked to study group". So, the primary endpoint was measured with blinding and minimised detection bias. No mention of blinding of radiology assessments, which were secondary outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	At 3 months, 109 of the 118 participants (92.3%) were assessable for DTCs, which is the primary endpoint. At 12 months, only 79 participants (67%) were assessable for DTCs. A negative outcome was assigned to participants with missing data points. For all other outcomes of interest in this review, there were no significant differences in attrition between the groups and reasons for any withdrawal were provided.
Selective reporting (reporting bias)	Low risk	All pre-specified endpoints were addressed. RFS data were also included
Other bias	Unclear risk	DTCs is a difficult endpoint, which may or may not correlate directly with clinically evident bone metastases. It was therefore not included in the formal meta-analysis

AREDIA 1998

Methods	Pooled updated report (2000) from 2 prospective, multicentre, randomised, double-blind, placebo-controlled studies
Participants	N = 751 Women with stage IV BC and osteolytic bone metastases
Interventions	2-h infusion of iv pamidronate 90 mg or placebo every 3-4 weeks for up to 24 cycles Protocol 18: participants receiving stable endocrine regimen at study entry. Protocol 19: participants receiving cytotoxic chemotherapy at study entry
Outcomes	Skeletal morbidity rate (events/year), bone pain, analgesic use, QoL (Spitzer scale), ECOG performance status, bone biochemical markers, time to first skeletal complication and survival. Skeletal complications are defined as radiation to bone, pathological fractures, surgery to bone, spinal cord compression or hypercalcaemia
Notes	AREDIA Protocol 18 (n = 372) published separately in Theriault 1999. Aredia Protocol 19 (n = 382), two-year results, was published separately in June 1998 by Hortobagyi in Journal of Clinical Oncology. Pooled analysis performed after testing for heterogeneity between studies 18 and 19 (or for having a SRE) using Breslow Day Test indicated homogeneity (P = 0.19) Analysis by ITT

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Assigned randomly in equal numbers with computer-generated randomisation list"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias)	Low risk	Double-blind (patients and study personnel): "infusions were prepared by the study pharmacist at each site according to a site specific, computer-generated randomisation list"

AREDIA 1998 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Other study personnel, as well as the patients and investigators, remained unaware of the treatment assigned. Double-blind study drug administration was continued throughout the entire course of the study for each participant. The radiologic bone surveys were reviewed by a central radiologist who was unaware of the treatment assignment of individual participants.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 115 of 367 participants (31.1%) in the pamidronate group and 100 of 387 participants (25.8%) in the placebo group completed 24 months of study ITT analysis was performed for the entire randomised population. All participants were included in the survival and safety analyses.
Selective reporting (reporting bias)	Low risk	All pre-specified endpoints were addressed
Other bias	Low risk	Study appeared to be free of other sources of bias

AZURE 2014

Methods	AZURE 2014 (BIG 01/04), adjuvant zoledronic acid study. Academic study run by the National Institute for Health Research National Cancer Research Network (NIHR NCRN) in the UK, involving 174 participating centres (UK, Ireland, Australia, Spain, Portugal, Thailand and Taiwan)
Participants	N = 3360 Women with resected stage II/III BC. 205 women with T3/4 disease or N1 disease who were undergoing neoadjuvant chemotherapy were recruited to the neoadjuvant arm study. Baseline characteristics: similar between groups. T3/4 (17.1% zoledronic acid, 17% no zoledronic acid); N2/3 (36.2% zoledronic acid, 35.9% no zoledronic acid); endocrine therapy alone (4.5% both arms), chemotherapy alone (21.5% both arms). Endocrine plus chemotherapy (73.9% zoledronic acid, 74.1% no zoledronic acid)
Interventions	Randomised to receive systemic adjuvant therapy +/- intervention: concurrent zoledronic acid iv over 15 min every 3-4 weeks for 6 doses, every 3 months for 8 doses, then every 6 months for 5 doses or no zoledronic acid, for the duration of 5 years. Participants on the neoadjuvant arm sub-study were randomised to standard neoadjuvant chemotherapy +/- zoledronic acid 4 mg every 3-4 weeks for 6 doses. Postoperatively, participants randomised to active arm continued on zoledronic acid every 3 months for 8 doses then 6 months for 5 doses
Outcomes	Primary endpoint: DFS (chest wall recurrence + regional recurrence + distant recurrence + death without recurrence) Secondary endpoints: invasive DFS, OS, BMFS, safety, translational endpoints
Notes	Statistics: statistically powered (20% beta and 5% alpha) to detect a 17% reduction in DFS with a lower boundary of efficacy of 0.833 and upper boundary of lack of efficacy of 0.936. ITT analysis. Follow-up: 59 months (Coleman 2010; see AZURE 2014). Trialists also kindly provided unpublished trial data to the Cochrane Review team.

Risk of bias

Bias	Authors' judgement	Support for judgement

AZURE 2014 *(Continued)*

Random sequence generation (selection bias)	Low risk	Minimisation method
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The primary end point of the study was DSF. The secondary end point was OS. Unlikely to be affected by bias. The follow-up schedule for both the zoledronic acid group and the control group included clinical assessment, physical examination, monitoring for adverse events, and measurement of hematologic, renal, and hepatic function. Investigations for possible recurrence were clinically directed as deemed appropriate by the treating physician. Routine follow-up imaging was not mandated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis. Only 2/681 participants (0.1%) in the zoledronate group had missing data
Selective reporting (reporting bias)	Low risk	All major endpoints addressed. Translational endpoint not yet reported
Other bias	Low risk	Study appeared to be free of other sources of bias

Body 2003

Methods	Double-blind, placebo-controlled study
Participants	N = 466 Women with BCBM
Interventions	iv ibandronate: 2 mg injection or 6 mg by 1-2 hr infusion or placebo injections or infusions monthly for up to 2 years
Outcomes	Bone events: pathological fractures, hypercalcaemic episodes, bone complications requiring radiotherapy or surgery. Average SREs per person, time to first SRE, proportion of participants experiencing ≥ 1 SRE, time periods without SRE, QoL assessed using EORTC-QLQ-30 scale, bone pain assessed using a 5-point scale, survival
Notes	Event rate results expressed as events per patient year. Results are from abstract presentation (Body 1999). Updated complete study is in preparation for publication

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomised". Baseline characteristics were similar between groups so randomisation appeared to be achieved
Allocation concealment (selection bias)	Unclear risk	No information provided

Body 2003 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded to placebo and ibandronate but not between 2 mg and 6 mg
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The primary outcome was number of 12-week periods with new bone complications and secondary outcomes were bone pain, analgesic use and safety. No mention of blinding of investigators when assessing vertebral fractures on radiographs
Incomplete outcome data (attrition bias) All outcomes	Low risk	Primary and secondary efficacy analyses were conducted using ITT population. Adverse events, death and refusal of treatment were the main reasons for withdrawals but these were similar across groups
Selective reporting (reporting bias)	Low risk	All pre-specified and expected outcomes were reported
Other bias	Low risk	Study appeared to be free of other sources of bias

Body 2004

Methods	Pooled results from 2 double-blind, placebo-controlled studies (MF4414 and MF4434)
Participants	N = 564 Patients with BCBM
Interventions	Oral ibandronate 50 mg or ibandronate 20 mg or placebo for up to 96 weeks. Only ibandronate 50 mg and placebo data were reported. The original design included 20 mg and 50 mg oral ibandronate arms. The pooled data on the 50 mg and placebo arms has been published in full. Earlier reports had indicated superiority in the 50 mg ibandronate arm, making it the recommended dose for clinical use
Outcomes	Skeletal morbidity period rate (vertebral fractures, non vertebral fractures, irradiation to bone, surgery to bone) in aggregate and for each component evaluated by skeletal morbidity period rate, bone pain, QoL assessed using EORTC-QLQ-30
Notes	The primary study endpoint was skeletal morbidity period rate, which was the number of 12-week periods with new skeletal complications, divided by the total observation time in periods.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomised". Baseline characteristics were similar between groups; randomisation appeared to be achieved
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled

Body 2004 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis. Most frequent reasons for withdrawals were reported for both groups and the percentages of withdrawals were similar across both groups
Selective reporting (reporting bias)	High risk	Ibandronate 20 mg data were not reported
Other bias	Low risk	Study appeared to be free of other sources of bias

CALGB-70604 2015

Methods	Randomised, phase III study Baseline characteristics of the 2 groups were comparable
Participants	N = 1822 participants (breast n = 833, prostate n = 674, myeloma n = 270 and other n = 45) Advanced or metastatic BC, prostate cancer or myeloma
Interventions	Zoledronic acid iv 4 mg every 4 weeks for up to 2 years or zoledronic acid iv 4 mg every 12 weeks for up to 2 years
Outcomes	Primary: proportion of participants with ≥ 1 SRE within 2 years after randomisation Secondary: pain assessment (Brief Pain Inventory), ECOG status, ONJ, renal toxicity, skeletal morbidity rate, bone turnover assessed by serum N-telopeptide (NTX), proportion of participants having ≥ one SRE within 24 months after randomisation for the subgroup of participants with BC, prostate cancer and multiple myeloma
Notes	clinicaltrials.gov/ct2/show/NCT00869206 Data reported in abstract form

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomisation, parallel assignment". Baseline characteristics were comparable between groups; randomisation appeared to be achieved
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided about outcome assessors
Incomplete outcome data (attrition bias)	Unclear risk	The abstract states that 833 participants were included but reports data only on 820 participants. No further details provided

CALGB-70604 2015 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Unclear risk	The conference abstract reports most of the outcomes per the clinical trials registry record except for pain intensity score, ECOG performance status and skeletal morbidity rate.
Other bias	Unclear risk	No information, information only available in abstract form

Conte 1996

Methods	Open-label, randomised, controlled study
Participants	N = 295 Female BC patients with lytic or mixed lytic/sclerotic bone metastases
Interventions	Chemotherapy or chemotherapy and iv pamidronate 45 mg every 3 weeks until progressive disease in bone
Outcomes	Time to progressive bone disease, bone pain, complications of bone metastases (hypercalcaemia, pathological fractures, episodes of radiotherapy or surgery), sclerotic response, analgesic use, response of extraskeletal metastases, WHO performance status
Notes	A blinded, extra-mural review was undertaken in each country. The results at extra mural review were referred to in this review. 83 participants included in efficacy analysis by ITT. 224 of these assessed at extra-mural review. 268 participants had baseline pain scores. All 295 evaluated for survival

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomised". Baseline characteristics were similar between groups; randomisation appeared to be achieved
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants remained in the active phase of the trial until they developed progressive disease in bone on radiograph and/or bone scan. Progressive disease in bone was diagnosed by a designated trial radiologist at each centre who was unaware of the participant's treatment. Participants were also discontinued if they developed a calcium level > 2.75 mmol/L that required specific therapy, or if they received corticosteroids for > 3 weeks.
Incomplete outcome data (attrition bias) All outcomes	High risk	12 participants excluded from the efficacy analysis (6 per arm), ITT analysis was "not feasible for these patients" as no imaging (6), no bone metastases at external review (2), baseline X-rays performed 2 months prior to randomisation (2), no treatment (1) and pamidronate given for hypercalcaemia (1)
Selective reporting (reporting bias)	Low risk	All endpoints addressed

Conte 1996 *(Continued)*

Other bias	Low risk	Study appeared to be free of other sources of bias

Diel 1998

Methods	Adjuvant study. Randomised, non-placebo-controlled study. Single-institution study (University Hospital Heidelberg 1990-1995)
Participants	N = 302 T1-T4, N0-2 primary BC with positive immunocytochemical detection of tumour cells in bone marrow. Baseline characteristics: similar between groups. T3 and T4 (17% clodronate, 16% no clodronate), node-positive disease (51% clodronate, 54% no clodronate), endocrine therapy alone (41% clodronate, 38% no clodronate), chemotherapy alone (25% clodronate, 28% no clodronate), combination therapy (16% clodronate, 15% no clodronate)
Interventions	Oral clodronate 1600 mg orally/d for 2 years or no clodronate. Adjuvant systemic therapy based on German Adjuvant Breast Cancer Group/St Gallen Consensus Conference guidelines
Outcomes	Primary endpoints: incidence of distant metastases: bone and visceral Secondary endpoints: length of time to bone and visceral metastases, OS
Notes	Statistics: study was powered to detect 10% difference between study groups Follow-up: examination every 3-4 months during the 2-year period. Chest radiographs, bone scans, liver ultrasound and mammography carried out annually. ITT analysis. Median follow-up of 8.5 years (Diel 2008)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned". Baseline characteristics were similar between groups; randomisation appeared to be achieved
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The pattern of metastasis was analysed at the end of the study. Bone lesions seen on radiographs were assessed by 2 independent radiologists
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/145 participants in the control group and 15/157 participants in the clodronate group were excluded with reasons provided. All participants were included in ITT analysis
Selective reporting (reporting bias)	Low risk	All endpoints reported; 3rd analysis to date (103 months' follow-up) which includes 290 of the original 302 participants
Other bias	Low risk	Study appeared to be free of other sources of bias

Diel 1999

Methods	Randomised, open-label, multicenter comparison study
Participants	N = 361 Women with BC with osteolytic bone metastases
Interventions	Clodronate 2400 mg/d orally or 900 mg clodronate iv every 3 weeks or 60 mg pamidronate iv every 3 weeks, over 2 years
Outcomes	Skeletal complications: vertebral fractures, pain; adverse events
Notes	The intervention was in addition to the participant's usual cytotoxic regimen. Results presented in abstract form only (Diel 1999). 318 participants evaluated after a median follow-up of 18 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomised". No baseline characteristics information given in the abstract
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given about outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information
Selective reporting (reporting bias)	Unclear risk	No information
Other bias	Unclear risk	No information, information only available in abstract form

E-ZO-FAST 2012

Methods	Phase III, randomised, 1:1 open-label study
Participants	N = 527 Postmenopausal women with early-stage (surgically resectable stage I, II, or IIIa) ER and/or PgR receptor–positive BC as well as baseline LS and TH T scores of 2.0 or greater, who had been on adjuvant letrozole 2.5 mg daily for 5 years No baseline characteristics were reported, except for no adjuvant chemotherapy (47.5% upfront group, versus 47.0% delayed group)

E-ZO-FAST 2012 *(Continued)*

Interventions	Upfront: zoledronic acid 4 mg every 6 months for 5 years Delayed start: triggered by post-baseline LS or TH T score decreased to < -2.0; any clinical, nontraumatic fracture; or asymptomatic vertebral fracture identified at 36 months), zoledronic acid 4 mg every 6 months for 5 years
Outcomes	Primary endpoint: percentage change in LS BMD at 12 months Secondary endpoints: percentage change difference in TH BMD from baseline to each assessment, 3-year fracture incidence, time to disease recurrence (local relapse or distant metastasis), OS, and safety
Notes	Statistics: this was predominantly a BMD study with disease recurrence as one of its pre-specified endpoints. 12-month follow-up reported. ITT analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were centrally randomised, using an interactive voice-response system, to either immediate zoledronate, which was initiated along with adjuvant letrozole, or to delayed zoledronate, to be initiated only after 1 of the following events was reported"
Allocation concealment (selection bias)	Low risk	Interactive voice-response system used
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given about outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis (Coleman 2009). Similar drop-out rates across groups at 12 months with reasons provided. Immediate zoledronate acid: 13.5%; delayed zoledronate acid: 12.6%
Selective reporting (reporting bias)	Low risk	All pre-specified and expected outcomes were reported
Other bias	Low risk	Study appeared to be free of other sources of bias

Elomaa 1983

Methods	Randomised, placebo-controlled study
Participants	N = 34 Women with BC with osteolytic bone metastases
Interventions	Oral clodronate (Cl2MDP) 1600 mg daily for 1 year or oral placebo
Outcomes	Bone mineralisation, hypercalcaemia, incidence of new bone metastases, fractures

Elomaa 1983 *(Continued)*

Notes	Basic cancer therapy consisted of tamoxifen in all participants. Chemotherapy was added during the course of the trial in 16/17 participants per arm for progressive disease. Initial findings were reported in Elomaa 1983. Updated reports were in Elomma 1987 and Elomaa 1988

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly allocated". No information was given about baseline characteristics
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Single-blinded: "placebo"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given about outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information
Selective reporting (reporting bias)	Unclear risk	No information. Endpoints were not specified
Other bias	Unclear risk	Unclear

Fizazi 2009

Methods	Phase II trial of denosumab in people with bone metastases from BC, prostate cancer and multiple myeloma. Second-line trial. Bone marker study. 26 centres in Europe and North America. Open-label trial
Participants	N = 111 (N = 46 for BC subgroup) Patients with BC, prostate cancer with bone metastases and multiple myeloma, who had high urinary N-telopeptide (uNTx) (> 50 nM) despite iv bisphosphonate treatment > 8 weeks. Exclusion criteria included > 2 SRE, radiotherapy to bones within 2 weeks, radioisotopes to bones within 8 weeks, unresolved toxicities (> grade 2)
Interventions	iv bisphosphonates every 4 weeks x 6 (clinician's choice: zoledronic acid or pamidronate) or sc injections of denosumab 180 mg every 4 weeks or denosumab 180 mg every 12 weeks for 25 weeks
Outcomes	Primary endpoint: proportion of participants with uNTx < 50 nM at week 13 Secondary endpoints: proportion of participants with uNTx < 50 nM at week 25, time to reduction of uNTx to < 50; duration of uNTx < 50; percent change of serum C-telopeptide (sCTx) from baseline to week 25, percent change of uNTx from baseline to week 25, incidence of hypercalcaemia; proportion of participants experiencing SREs, and the time to first on-study SRE, exploratory biomarker measurement

Fizazi 2009 *(Continued)*

Notes	Unpublished data of SRE endpoint from BC subgroup only was supplied by Amgen Pharmaceuticals, which enabled this study to be included and analysed Follow-up of 57 weeks (2 years' follow-up for optional ongoing extension phase study)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomized". Baseline characteristics were similar between groups; randomisation appeared to be achieved
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome was biochemical analysis, unlikely to be affected by knowledge of treatment group
Incomplete outcome data (attrition bias) All outcomes	High risk	2 participants did not receive bisphosphonates, and 1 participant did not receive denosumab. 4 participants in denosumab group did not have uNTx measurement post-baseline. These were not included in final efficacy analysis (non-ITT analysis)
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported
Other bias	Low risk	Study appeared to be free of other sources of bias

GAIN 2013

Methods	Phase III, open-label, 2 x 2 factorial design
Participants	N = 2994 BC, N1-2, M0, post-surgery
Interventions	Randomisation A: (A1) sequential epirubicin-taxol-cyclophosphamide or (A2) epirubicin-cyclophosphamide Taxol-Xeloda Randomisation B: (B1) ibandronate 50 mg/d for 2 years or (B2) no ibandronate
Outcomes	Primary endpoint: DFS (A1 versus A2, B1 versus B2) Secondary endpoint: OS, event-free survival in hormone sensitive/insensitive subgroups and N0, compliance, safety (A1 versus A2, B1 versus B2), rate of responders, incidence of primary (A1 versus A2), prognostic markers
Notes	Trialists kindly provided unpublished data on study outcomes by menopausal status.

Risk of bias

GAIN 2013 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated permutated block randomisation" p3535 2:1 randomisation ibandronate (n = 2015) to observation (n = 1008)
Allocation concealment (selection bias)	Low risk	"Eligibility was centrally confirmed ... computer-generated permutated block randomization" p.3535
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given about outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Modified ITT analysis. Analysis conducted on those commencing study treatment. Very small number of participants did not commence treatment & were excluded from ITT analysis (ibandronate 19/2015 = 0.9%; observation 10/1008 = 1%)
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes of ibandronate analysis reported. Analysis relating to randomisation A to be reported in companion paper.
Other bias	Low risk	Study appeared to be free of other sources of bias.

Heras 2009

Methods	Randomised, double-blind, placebo-controlled trial
Participants	N = 150 BCBM Baseline characteristics: only demographics described. No comparison of baseline characteristics between treatment and control arms
Interventions	6 mg iv ibandronate or placebo every 4 weeks for 24 months
Outcomes	Primary endpoint: proportion of participants with SRE (defined as pathologic fracture, spinal cord compression, radiation therapy to bone, change in anti-neoplastic therapy and surgery to bone) Secondary endpoints: time to first SRE, skeletal morbidity rate (events/year) and time to progression of bone lesions.
Notes	Statistics: limited information about power and target HR. Alpha value of 5% was taken for consideration of statistical significance Other treatment and follow-up: not described

Risk of bias

Bias	Authors' judgement	Support for judgement

Heras 2009 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"Randomized". Baseline characteristics restricted to description of demographics between treatment arms only
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were probably blinded. Primary efficacy end point was the proportion of participants with SREs, which were defined as pathologic fracture, spinal cord compression, radiation therapy to bone, change in anti-neoplastic therapy and surgery to bone
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information about missing data or ITT analysis
Selective reporting (reporting bias)	Unclear risk	All pre-specified endpoints were reported. However, safety was only briefly described without the complete list of AEs
Other bias	Low risk	Study appeared to be free of other sources of bias

Hershman 2008

Methods	Phase III, randomised, double-blind, multicentre trial
Participants	N = 114 Pre-menopausal early BC women on adjuvant chemotherapy Baseline characteristics: majority stage II patients (slightly more stage I in placebo group 38% versus 29%, more stage II in treatment group 67% versus 54%), 66% hormone receptor-positive
Interventions	iv zoledronic acid 4 mg every 3 months or placebo for 12 months Other treatment: 80% on chemotherapy, 60% on tamoxifen, 26% on aromatase inhibitors. All participants on calcium and vitamin D
Outcomes	Primary endpoint: LS BMD at 24 and 52 weeks after initiation of chemotherapy Secondary endpoints: Percentage change in TH and femoral neck BMD, changes in CTX (serum C-telopeptide of type I collagen, a marker of bone resorption) and BSAP (bone-specific alkaline phosphatase, a marker of bone formation) at 24 and 52 weeks
Notes	Statistics: study was 90% powered (5% alpha) to detect a difference of 3% change in LS BMD Per-protocol analysis (114 randomised, 85 completed 12-month evaluation)
Risk of bias	

Hershman 2008 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random permutated block
Allocation concealment (selection bias)	Low risk	Central site enrolment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis. Reasons were provided for participants who withdrew from the study and were generally similar across groups
Selective reporting (reporting bias)	High risk	All pre-specified endpoints were addressed. However, recurrence was not actually an endpoint but was mentioned. Since recurrence was mentioned in the manuscript, we included this study. However, it was unlikely that the study was powered to detect difference in recurrence between arms.
Other bias	Low risk	Study appeared to be free of other sources of bias

Hultborn 1999

Methods	Randomised, placebo-controlled multi-centre study
Participants	N = 404 Women with BC with skeletal metastases and expected survival > 3 months
Interventions	iv pamidronate 60 mg every 3-4 weeks up to 2 years or iv placebo
Outcomes	SREs (symptoms e.g. pain, hypercalcaemia, fractures, radiotherapy, surgery, change in antitumoural therapy)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Random permutated blocks of 6"
Allocation concealment (selection bias)	Low risk	"Numbered packages"
Blinding of participants and personnel (performance bias)	Low risk	"The packages are delivered to hospital pharmacy with package number and patient identification to the study centre". All pharmacy staff, nurses, physi-

Hultborn 1999 *(Continued)*

All outcomes		cians and patients were blinded to treatment. Blinded treatment was not uncoded at treatment discontinuation unless the SAE was reported"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The incidence of skeletal symptoms events (e.g. fractures, hypercalcaemia) was recorded every 3 months but the article did not describe by whom. The article also described "all medication was also recorded by a nurse"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were analysed. No missing outcome data reported
Selective reporting (reporting bias)	Low risk	All pre-specified endpoints were reported
Other bias	Low risk	Study appeared to be free of other sources of bias

Kanis 1996

Methods	Randomised, double-blind, placebo-controlled study
Participants	N = 133 Women with recurrent BC but no skeletal metastases
Interventions	Oral clodronate 1600 mg daily for 3 years or identical oral placebo
Outcomes	Incidence of skeletal metastases, complications of skeletal metastases e.g. hypercalcaemia, bone pain, fractures
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly allocated". Baseline characteristics were similar between groups so randomisation appeared to be achieved
Allocation concealment (selection bias)	Low risk	Randomisation was controlled at an independent centre, pre-randomisation numbering system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Single-blinded with an identical placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Bone scintigraphy and skeletal X-rays (hands, pelvis, skull, lateral lumbar, and thoracic spine) were obtained at 6-month intervals and read blindly
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were analysed. "No significant difference in the number of patients withdrawn from the study" between groups (p. 664)
Selective reporting (reporting bias)	Low risk	All pre-specified endpoints were reported

Kanis 1996 *(Continued)*

Other bias	Low risk	Study appeared to be free of other sources of bias

Kohno 2005

Methods	Multicentre, randomised, double-blind, placebo-controlled study.
Participants	N = 228 Japanese women with stage IV BC with ≥ 1 osteolytic bone metastasis
Interventions	iv zoledronic acid (4 mg) or placebo every 4 weeks for 12 months
Outcomes	SREs, incidence, rate, time-to-event; toxicity and pain
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomised with dynamic balancing method"
Allocation concealment (selection bias)	Low risk	Registered by facsimile and verified by central office, which then contacted the individual centre
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All radiologic assessments, including vertebral fractures, were conducted by a blinded radiographic assessment committee
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were analysed except for 1 participant in the placebo group (with reason provided)
Selective reporting (reporting bias)	Low risk	All pre-specified endpoints were reported
Other bias	Low risk	Study appeared to be free of other sources of bias

Kristensen 1999

Methods	Prospective, randomised, controlled, open-label study
Participants	N = 100 BCBM
Interventions	Oral clodronate 800 mg twice/d for 2 years or open control

Kristensen 1999 *(Continued)*

	The dose of clodronate was increased to 1600 mg twice/d at first progression in bone and therapy was stopped if subsequent bone progression occurred. The intervention was in addition to underlying systemic treatment for BC: chemotherapy, endocrine therapy or both
Outcomes	SREs (hypercalcaemia, fractures, radiotherapy), pain, QoL. QoL was assessed using the EORTC-QLQ-C30
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation (blocks of 10) by computer-generated randomisation list
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open control
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided about outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were analysed except for 1 participant who was excluded from the statistical analysis because the diagnosis of bone metastases remained unsettled
Selective reporting (reporting bias)	Low risk	All pre-specified endpoints were reported
Other bias	Low risk	Study appeared to be free of other sources of bias

Kristensen 2008

Methods	Open-label, randomised, controlled study. Participants recruited from Denmark, Sweden and Iceland from 1990-1996
Participants	N = 953 Women with resectable adenocarcinoma of the breast and without distant metastases, in 3 groups: pre-menopausal women with grade II/III malignancy, without lymph node metastases and primary tumour ≤ 5 cm, independent of hormone receptor status pre-menopausal women with axillary lymph node metastases or primary tumour > 5 cm, with negative hormone receptor status post-menopausal women with axillary lymph node metastases or primary tumour > 5 cm, with negative hormone receptor status

Kristensen 2008 *(Continued)*

	Baseline characteristics: similar between treatment arms. > 70% axillary lymph node with metastases; > 20 mm: 57% pamidronate, 57% control; Grade 3: 37% pamidronate, 39% control; ER-positive: 13% pamidronate, 17% control Other treatment: adjuvant chemotherapy (cyclophosphamide, methotrexate and 5-fluouracil (CMF), or cyclophosphamide, epirubicin and 5-fluouracil (CEF)). Loco-regional radiotherapy as per local guidelines. Endocrine therapy was to be avoided.
Interventions	Oral pamidronate 150 mg twice/d for 4 years or no adjuvant therapy
Outcomes	Endpoints: SREs, safety, BMD, survival Primary versus secondary endpoints were not specified
Notes	Statistics: alpha, beta values and expected HRs were not specified. Multivariate analyses were performed between the 3 groups, tumour size, nodal status, type of surgery, histological type and grade, hormone receptor status, centre and treatment regimen Follow-up: for the first year, every 12 weeks a clinical visit. For years 2-5, every 6 months a clinical visit. For years 6-10, an annual visit. Routine biochemistry was measured at each treatment, at 24 and 48 weeks, then twice/year for 3 years. Pelvic and spinal X-rays were performed every 6 months and bone scans every year for 4 years. BMD was measured in a Swedish subgroup. 10 years of follow-up. Categorical DFS and OS outcome data not published. Study authors contacted for data, including by menopausal status. Trialists kindly provided unpublished trial data to the Cochrane Review team.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomized". Baseline characteristics were similar between groups; randomisation appeared to be achieved
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open control
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided about outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	In the pamidronate arm, 460 allocated with pamidronate, 450 assessed for bone recurrence, 337 assessed for fractures, all participants assessed for OS (417 treated as per protocol). In the control arm, 493 allocated with pamidronate, 469 assessed for bone recurrence, 365 assessed for fractures, all participants assessed for OS (467 treated as per protocol). Ten participants from pamidronate arm and 14 from control arm were lost to follow-up (˜3%). ITT analysis was performed and the results were similar to adjusted-for-protocol analysis
Selective reporting (reporting bias)	Unclear risk	Primary and secondary endpoints were not specified but both effects (recurrence, fracture, survival) and side-effects were reported
Other bias	High risk	Participants were not allowed to be on endocrine therapy. However, 17% of participants in control arm versus 13% in pamidronate arm were ER-positive.

Kristensen 2008 *(Continued)*

	This may potentially bias results against the control arm since these participants were not treated optimally

Lipton 2008

Methods	Double-blinded, active-controlled, randomised phase II trial. International trial with 56 centres involved in Europe, North America and Australia
Participants	N = 255 Women with BCBM, ECOG 0-2 Baseline characteristics: overall balanced between the 6 arms. Higher rate of no SRE in the arm with 180 mg every 12 weeks denosumab (80%), although there was no difference in the rate of SRE between bisphosphonate and total denosumab (65% versus 66%)
Interventions	Randomised 1:6 ratio to receive sc injection of denosumab (30 mg, 120 mg, 180 mg) or every 12 weeks (60 mg, 180 mg), or open-label iv bisphosphonate (zoledronic acid, pamidronate or ibandronate) every 4 weeks During the 32-week off-treatment period, participants could choose to receive iv bisphosphonate, which was considered standard of care therapy
Outcomes	Primary endpoint: percentage change of week 13 urinary NTx/Cr ratio from baseline Secondary endpoints: percentage change of week 26 urinary NTx/ Cr ratio from baseline, proportion of participants with > 65% reduction of NTx/Cr from baseline, median time to achieve this reduction, percentage of participants experiencing on-study SRE (defined as fracture, surgery or radiation to bone, or spinal cord compression), safety
Notes	Statistics: powered to detect a +/- 5.1% difference in primary endpoint with 95% CI Follow-up: throughout the treatment period, serum chemistries and denosumab concentrations, urinary NTx/Cr levels were measured periodically. Off-treatment, there were 4 visits for assessment of NTx/Cr level and safety. Total follow-up period of 57 weeks (25 weeks of treatment and 32 weeks of follow-up)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomized". Baseline characteristics were similar between groups; randomisation appeared to be achieved
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Partially double-blind". Participants received either sc denosumab and placebo to maintain blinding to the dose, or iv infusion of bisphosphonate
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The primary end point of the study, reported previously, was the percentage change from baseline to week 13 in uNTx/Cr (16). Additional efficacy end points were the percentage change from baseline to week 25 in uNTx/Cr, the proportion of patients who achieved a >65% reduction in uNTx/Cr from baseline, and the median time to achieve this reduction. The percentage of patients experiencing an SRE (fracture, surgery or radiation to bone, or spinal

Lipton 2008 *(Continued)*

		cord compression) while on the study was also evaluated. No mention of blinding of outcome assessment, but unlikely to influence outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	12% of iv bisphosphonate group and 6% of denosumab group discontinued their trial by week 13 analysis of primary endpoint; 30% of iv bisphosphonate group and 33% of denosumab group did not continue to week 57 final assessment. Neither CONSORT diagram nor explicit information about how missing data was addressed were available
Selective reporting (reporting bias)	Low risk	All the bone marker endpoints, SRE and safety parameters were reported
Other bias	Unclear risk	This was akin to a dose-finding extended phase Ib/II trial. Whilst the primary endpoint urinary NTx/Cr at 13 weeks was reported separately for bisphosphonate and each of the 5 doses of denosumab, the secondary SRE endpoint was reported in aggregate (bisphosphonate vs all doses for denosumab). The standard dose of denosumab was now recognised at 120 mg monthly. It was difficult to know from this trial the true effect of standard-dose denosumab against zoledronic acid

Mardiak 2000

Methods	Randomised, placebo-controlled trial
Participants	N = 73 Women with BC with previously untreated locally advanced disease or metastases but no bone or central nervous system metastases 90% had stage III disease 65% of participants received chemotherapy, 14 % received hormonal therapy, 23 % received both
Interventions	Oral clodronate 800 mg twice/d or placebo for 2 years
Outcomes	Incidence of bone and visceral metastases, time to progression, survival
Notes	10 participants not evaluable because of treatment < 2 months

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomised", no other information provided
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind with placebo

Mardiak 2000 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind. Bone scans were taken every 6 months or earlier if the participant was symptomatic. The outcomes were bone metastases, visceral metastases or death.
Incomplete outcome data (attrition bias) All outcomes	High risk	10/72 participants not evaluable because of "short duration of therapy (2 months)"
Selective reporting (reporting bias)	Low risk	All pre-specified and expected outcomes were reported
Other bias	Low risk	Study appeared to be free of other sources of bias

Martoni 1991

Methods	Randomised, open-label study, placebo-controlled in the first week only during iv phase of treatment
Participants	N = 38; N = 33 evaluated Normocalcaemic women with BCBM
Interventions	Clodronate (Cl2MDP) 300 mg/d/iv or placebo for 7 d, then clodronate 100 mg/d/im for 3 weeks followed by 100 mg/im on alternate days for ≥ a further 2 months or no additional treatment Treatment was in addition to specific anti-tumour therapy
Outcomes	Laboratory tests of calcium metabolism, bone pain and radiological response (X-rays and bone scan). The incidence of hypercalcaemia and fractures was recorded in evaluable participants. Pain was assessed during the first week using the Scott-Huskisson visual-analogue method
Notes	Skeletal endpoints were described in 21/33 evaluable participants

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomised". Baseline characteristics were similar between groups; randomisation appeared to be achieved
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Placebo was administered, but at different regimen to treatment, so it was not effectively blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Biochemical tests were completed and unlikely to be influenced by the lack of blinding. However the other outcome measures were self-reported pain intensity and number of bone lesions that may have been affected by no blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two participants from arm A and 1 participant from arm B were not evaluated, but it was a negligible number. No ITT analysis

Martoni 1991 *(Continued)*

Selective reporting (reporting bias)	Low risk	All pre-specified and expected outcomes were reported
Other bias	Low risk	Study appeared to be free of other sources of bias

NATAN 2016

Methods	Randomised, controlled, phase III (open label). Germany and Austrian study
Participants	N = 693 (enrolment) Participants with residual invasive tumour (ypT1-4 and/or ypNþ) after ≥ 4 cycles of anthracycline-taxane-containing neoadjuvant chemotherapy
Interventions	Zoledronate 4 mg iv for 5 years or observation. Zoledronate was given every 4 weeks for the first 6 months, every 3 months for the following 2 years, and every 6 months for the last 2.5 years
Outcomes	Primary outcome: DFS Secondary outcomes: event-free survival with respect to interval between surgery and randomisation, BMFS, OS, predictive value of primary breast tumour response to postoperative treatment, prognostic impact of chemotherapy induced amenorrhoea in premenopausal women, toxicity
Notes	Trialists also kindly provided unpublished trial data to the Cochrane Review team.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patients eligibility was centrally confirmed and block randomisation was used to randomise the patients after stratification for centre, time interval between surgery and entering the clinical trial (within 3 months, within 1 year, within 2 years, within 3 years), age at study entry (<50, or >50 years) and receptor content in diagnostic core or surgical biopsy"
Allocation concealment (selection bias)	Low risk	Block randomisation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcomes were DFS, OS and toxicity. OS and DFS endpoints are less likely to be affected by unblinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low loss to follow-up (1.5%); similar in both arms. Analyses were ITT
Selective reporting (reporting bias)	Low risk	Outcomes listed in the prospectively registered trial (NCT00512993) were covered in the clinical trial report
Other bias	Low risk	Study appeared to be free of other sources of bias

NSABP-34 2012

Methods	Multicentre, randomised, double-blind, placebo-controlled study. Local & systemic treatment at discretion of investigators
Participants	N = 3323 Operable stage I-III BC (T1-3, N0-2, M0). Age ≥ 50 years (65%); white (83%). T1 (67%), T2 (27%); N0 (75%), N1 (18%), N2 (6%) ER and/or PgR positive (78%), ER/PR negative (22%) Endocrine alone (31%), chemo alone (21%), both (44%)
Interventions	Clodronate 1600 mg/d for 3 years (n = 1662) or placebo (n = 1661)
Outcomes	Primary endpoint: DFS Secondary endpoints: skeletal metastases, OS, RFS, incidence of non-skeletal metastases
Notes	Poor adherence - by the "end of the 3-year therapeutic period, 60% (992/1647) of women assigned placebo and 56% (919/1640) of those allocated clodronate remained on study drugs " p737 Median follow up 90 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified randomisation with a biased-coin minimisation approach to generate a treatment assignment on entry Stratified participants (within every centre) by age (< 50 and ≥ 50 years), number of positive axillary nodes (0, 1–3, and ≥ 4), and hormone receptor status (both ER and PgR negative, or one or both receptors positive)
Allocation concealment (selection bias)	Low risk	"Biased coin minimisation approach on study entry "p735
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All participants, clinicians who treated and assessed protocol doctors were masked to treatment group assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis. Very small number excluded as lost to follow-up: clodronate: 7/1662; placebo: 5/1661
Selective reporting (reporting bias)	Low risk	All primary and secondary endpoints reported
Other bias	Low risk	Study appeared to be free of other sources of bias

OPTIMIZE-2 2014

Methods	Prospective, randomised, double-blind, multicenter non-inferiority trial
Participants	N = 433 Women with bone metastases from BC who previously received ≥ 9 doses of iv bisphosphonates (zoledronic acid or pamidronate) during the first 10-15 months of therapy Baseline characteristics were comparable between arms
Interventions	Randomised (1:1) to receive zoledronate iv 4 mg every 4 week or every 12 weeks (placebo between zoledronate doses to maintain blind) for 1 year
Outcomes	Primary: proportion of participants who experienced ≥ 1 SRE. Primary analysis was non-inferiority (predefined margin of 10%) for the difference in SRE rates Secondary endpoints: time to first SRE, skeletal morbidity rate (SMR), bone pain score, change in bone turnover markers, and safety
Notes	Conference abstract: Hortobagyi 2014 clinicaltrials.gov/ct2/show/study/NCT00320710?sect=X30156: outcome data including adverse events are included in trial registry record

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomised" with no further details provided. Baseline characteristics were comparable between groups; randomisation appeared to be achieved
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double blind (participant, investigator)" as per clinical trial registry record
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The number of participants who completed the study did not match the denominators for certain outcomes (e.g. bone pain). Awaiting details from full trial publication
Selective reporting (reporting bias)	Low risk	All outcomes reported in the trial registry record; if not, reasons were provided (e.g. too few events to report median)
Other bias	Low risk	Appears to be free of other sources of bias

Paterson 1993

Methods	Double-blind placebo-controlled trial.
Participants	N = 173 (updated data provided for N = 185)

Paterson 1993 *(Continued)*

	Patients with BCBM
Interventions	Oral clodronate 800 mg twice/d or placebo for 3 years
Outcomes	Hypercalcaemia, fractures and radiotherapy required for bone pain
Notes	Analysis by ITT

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Pre-randomized numbering system"
Allocation concealment (selection bias)	Low risk	Controlled by independent centre: "pre-randomized numbering system whereby patients, allocated a number in the order in which they presented, were prescribed the corresponding numbered medication package at each center at 3-month intervals"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled. The clinicians, nursing staff, and pharmacy staff at each participating hospital were unaware of the treatment allocation of participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Biochemical measures were the primary outcome. Nonvertebral fractures were diagnosed and recorded by the trial radiologists at each centre. A research assistant based at the University of Sheffield travelled to each centre to perform vertebral and metacarpal morphometry. Unlikely to be aware of treatment groups
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were analysed. The number of withdrawals were reported and similar across both groups
Selective reporting (reporting bias)	Low risk	All pre-specified and expected outcomes were reported
Other bias	Low risk	Study appeared to be free of other sources of bias

Powles 2006

Methods	Double-blind, placebo-controlled randomised study. Multi-national, multi-centred study
Participants	N = 1069 Pre- and post-menopausal women with primary operable BC Baseline characteristics: similar between groups. Median age (53 years for both groups), stage III (9% clodronate, 10% placebo), axillary lymph node involvement (37% clodronate, 38% placebo)
Interventions	Clodronate 1600 mg/d orally or placebo for 2 years
Outcomes	Primary endpoint: incidence of bone metastases over 5-year study period Secondary endpoints: OS, non-skeletal relapse

Powles 2006 *(Continued)*

Notes	Statistics: study was powered (5% beta, 5% alpha) to detect a 25% reduction in bone metastases over 5 years Analysis by ITT. Follow-up of 5.6 years (final analysis, Powles 2006) Follow-up: clinical laboratory tests every 3 months for the first year, every 6 months between 2-5 years. All participants were assessed for bone metastases at 2 years and 5 years (bone scan, skeletal X-ray, CT or MRI if indicated)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomized by means of numerically ordered and coded packages..."
Allocation concealment (selection bias)	Low risk	"Centralised blinded code"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The primary outcome was time to first bone metastases and secondary outcomes were OS and occurrence of skeletal relapses. "Bone metastases were diagnosed by isotopic bone scan, skeletal X-rays and CT or MRI if required. The final diagnosis of bone metastases and subsequent audits of the data were always performed blinded to the patient's study medication" (pg. 3)
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis. All participants included in the analysis and no missing outcome data
Selective reporting (reporting bias)	Low risk	All pre-specified and expected outcomes were reported
Other bias	Low risk	Study appeared to be free of other sources of bias

Rosen 2004

Methods	Double-blind phase III comparison study
Participants	N = 1130 Women with ABC and ≥ 1 bone metastasis and patients with stage III multiple myeloma
Interventions	iv zoledronic acid (4 mg or 8 mg) or pamidronate 90 mg iv every 3-4 weeks for 12 months Participants in the 8 mg zoledronic acid arm, had zoledronic acid subsequently reduced to 4 mg because of concern over possible toxicity
Outcomes	SREs: incidence at 13 months, morbidity, time-to-event, bone pain Stratified data on BC participants presented on proportion with any SRE at 13 months, bone markers and survival

Rosen 2004 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomised". Baseline characteristics were similar between groups; randomisation appeared to be achieved
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy infusions; double-blind, but pharmacists at each hospital were aware of the medications given
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcomes were proportion of participants who experienced ≥ 1 SRE, in addition to AEs, serious AEs and laboratory data. It is unlikely that any potential unblinding would affect the types of outcomes assessed
Incomplete outcome data (attrition bias) All outcomes	Low risk	99.7% of participants were analysed
Selective reporting (reporting bias)	Low risk	All pre-specified and expected outcomes were reported. Participants initially randomised to 8 mg zoledronic acid were given 4 mg after protocol amendment in 2000. The potential bias was mitigated by analysing the 4 mg zoledronic acid and 8 mg/4 mg zoledronic acid separately
Other bias	Low risk	Study appeared to be free of other sources of bias

Saarto 2004

Methods	Adjuvant clodronate study. Randomised, open-label, controlled trial. Single institution study (Helsinki University Hospital, Finland 1990-1993)
Participants	N = 299 (282 in analysis as 17 participants excluded from analysis due to major protocol violation) Women with primary operable node-positive BC. T1-3, N1-2, M0 Baseline characteristics: similar between groups. Median age (52 years for both groups), T3 (6% of all participants), N2/3 (24% of all participants), adjuvant chemotherapy (54%), adjuvant endocrine therapy (46%) Other treatments: all participants received post-operative radiotherapy (50 Gy/25 fractions) to breast and regional lymph nodes, and adjuvant systemic therapy: premenopausal 6 cycles CMF and postmenopausal anti-oestrogens (randomised to tamoxifen or toremifene for 3 years)
Interventions	Clodronate 1600 mg daily for 3 years or open control
Outcomes	Primary endpoint: incidence of bone metastases (and visceral metastases) Secondary endpoints: survival, DFS Follow-up: bone scan at 1, 2, 3, 5 and 10 years. Clinical investigation and laboratory tests every 4-6 months for the first 5 years and at 10-year visit

Saarto 2004 *(Continued)*

Notes	Statistics: study was powered (beta 20%) to detect a 10% to 15% difference between arms Analysis by ITT. 10-year follow-up data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomized". Baseline characteristics were similar between groups; randomisation appeared to be achieved
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Clinical investigation and basic laboratory tests were repeated every 4 to 6 months with a radiologic examination if necessary. Investigators performing bone scans and radiologic examinations were blinded to treatment allocation" (pg.11)
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT. No missing data for the final population of 282
Selective reporting (reporting bias)	Low risk	Outcomes were not specified in methodology; however, all expected outcomes were reported
Other bias	Low risk	Study appeared to be free of other sources of bias

Stopeck 2010

Methods	Randomised, phase III trial. International trial involving 322 centres in Europe, North America, America, South America, Japan, Australia, India and South Africa. Double-blind, double-dummy, active controlled trial
Participants	N= 2049 Women with BC with prior or current radiological evidence of ≥ 1 bone metastasis, ECOG 0-2 Baseline characteristics: similar between groups. 37% of participants in each group had prior SRE. Oestrogen receptor/progesterone receptor-positive in 71% of participants on zoledronic acid, 72% of participants on denosumab, HER2 in 18% of participants in both groups. 21% of participants in each group had lung metastases, 18% (zoledronic acid) and 21% (denosumab) participants had liver metastases Other treatment: all chemotherapy and hormonal therapies were allowed
Interventions	Randomised to sc denosumab 120 mg and iv placebo every 4 weeks, or iv zoledronic acid 4 mg and sc injection of placebo every 4 weeks
Outcomes	Primary endpoint: first on-study SRE (non-inferiority test). SRE was defined as pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression)

Stopeck 2010 *(Continued)*

	Secondary endpoints: first on-study (superiority test), time to first and subsequent on-study SREs, safety endpoint. Follow-up: clinic visits every 4 weeks with skeletal surveys (X-rays) every 12 weeks to assess fractures. Other radiological assessments (CT or MRI) are allowed as part of standard care. All radiological assessment were confirmed by 2 radiologists independently through blinded central radiology review
Notes	Statistics: the study was 97% powered with 95% confidence (alpha 5%, beta 3%) to detect its non-inferiority endpoint, set at HR of 0.9. The study was 90% powered with 95% confidence (alpha 5%, beta 10%) to detect its superiority endpoint, set at HR of 0.8 ITT analysis. Follow-up of 34 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned". Baseline characteristics were similar between groups; randomisation appeared to be achieved
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blinded, double-dummy"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were SRE (defined as pathologic fracture, radiation therapy to bone, surgery to bone or spinal cord compression). "Fractures were assessed by skeletal surveys (x-rays) every 12 weeks or by radiographic assessments (x-ray, computed tomography, or magnetic resonance imaging) during the course of standard care and were identified or confirmed independently by ≥ two radiologists through blinded central radiology review". "Spinal cord compression events were also confirmed by blinded central radiology review" (pg. 5133)
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis. All participants included in efficacy analysis. Number of participants who discontinued were reported with no significant differences evidence between groups (as per CONSORT flowchart)
Selective reporting (reporting bias)	Low risk	All endpoints were reported
Other bias	Low risk	Study appeared to be free of other sources of bias

SWOG-S0307 2015

Methods	Randomised, controlled, phase III trial (open label). US study
Participants	N = 6097 participants Women with stage I-IIIa BC receiving adjuvant therapy. Median age: 53 years. 58% postmenopausal or aged ≥ 50 years
Interventions	Zoledronate iv 4 mg monthly for 6 months then 3-monthly for 30 months or oral clodronate 1600 mg/d 36 months or oral ibandronate 50 mg/d for 36 months

SWOG-S0307 2015 *(Continued)*

Outcomes	Primary outcomes: histological confirmation of disease recurrence, site of first disease recurrence, DFS, OS, Zubrod performance status Secondary outcomes: time to progression, tolerability, participant's compliance, bone markers, dental substudy
Notes	clinicaltrials.gov/ct2/show/NCT00127205

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were "randomised" but no further details provided in the abstracts
Allocation concealment (selection bias)	Unclear risk	No information provided in abstract
Blinding of participants and personnel (performance bias) All outcomes	High risk	No masking (as per clinical trials registry record)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided about outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Abstract states that analysis would be ITT but no further details provided
Selective reporting (reporting bias)	Unclear risk	Most outcomes reported in abstract form
Other bias	Unclear risk	Insufficient information to judge

Tevaarwerk 2007

Methods	Randomised, open-label study. Multicentre study in USA from 2000-2007
Participants	N = 68 Post-menopausal women with stage II/III adenocarcinoma of the breast
Interventions	Randomised to zoledronic acid 4 mg iv every 12 weeks for 4 cycles or observation Baseline characteristics: imbalance in the rate of T1 and T2 disease (T1: 39% zoledronic acid, 2% control; T2: 30% zoledronic acid, 56% control). Imbalance in the rate of N1 and N2/3 disease (N1: 41% zoledronic acid, 15% control; N2-3: 56% zoledronic acid, 78% control) Other treatment: adjuvant chemotherapy needed for 33/36 zoledronic acid and 31/32 control participants, and adjuvant radiation needed for 24/36 zoledronic acid and 26/32 control participants. Use of calcium and vitamin D were permitted but not mandated in the study
Outcomes	Endpoints: BMD measurement, toxicities DFS and OS

Tevaarwerk 2007 *(Continued)*

Notes	Statistics: the study was 80% powered with 0.05 alpha to detect a mean BMD change (lumbar spine) of ≥ 1.75% between zoledronic acid and observation ITT analysis. Follow-up of 8 years. Follow-up: BMD was measured at baseline, 6 and 12 months. Toxicity evaluated on day 1 in clinic and 1 week by telephone after treatment. Other ancillary tests as per clinician's discretion

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"Randomised", but baseline characteristics were very different between groups so randomisation was deemed to be not complete
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcomes were BMD (measured by DXA devices), death, disease recurrence and toxicity. "BMD results were reviewed by a single physician specializing in bone mass measurement" (p 3). The paper did not mention whether the physician was aware of treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis. In both arms, 6 participants did not complete the study with reasons provided
Selective reporting (reporting bias)	Low risk	Endpoints were not pre-specified, but all possible endpoints from a BMD trial were included. DFS and OS endpoints were provided by investigator from contacting first author
Other bias	Low risk	Study appeared to be free of other sources of bias

Tripathy 2004

Methods	Randomised 1:1:1, parallel-group, double-blind, placebo-controlled
Participants	N = 435 (Study MF4434) Patients with histologically confirmed BC and radiographically confirmed bone metastases
Interventions	3 arms: oral ibandronate 50 mg/d for 96 weeks (n = 148) oral ibandronate 20 mg/d for 96 weeks (n = 144) placebo (n = 143)
Outcomes	SREs reported, bone pain, analgesic use. SREs reported as Skeletal Morbidity Period Rate (SMPR)
Notes	

Tripathy 2004 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomised". Baseline characteristics were similar between groups; randomisation appeared to be achieved
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled, double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis. The percentage of early withdrawals was similar across groups
Selective reporting (reporting bias)	Low risk	All pre-specified and expected outcomes were reported
Other bias	Low risk	Study appeared to be free of other sources of bias

Tubiana-Hulin 2001

Methods	Double-blind, randomised, controlled study
Participants	N = 144 Patients with BC and osteolytic bone metastases
Interventions	Oral clodronate 1600 mg/d or placebo for up to 12 months
Outcomes	Time to bone event (hypercalcaemia, new bone pain, radiotherapy required to relieve bone pain, pathological fractures or death due to bone metastases), pain intensity. Pain intensity assessed using a visual pain scale
Notes	Publication in French

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomised". Baseline characteristics were similar between groups so randomisation appeared to be achieved
Allocation concealment (selection bias)	Unclear risk	No information provided

Tubiana-Hulin 2001 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided about outcome assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	7 participants not analysed (3 from placebo group, 4 from treatment group), including 1 in clodronate group that developed pulmonary lymphangitis 16 days after starting treatment, and 2 from placebo group who died from myocardial infarction and hypercalcaemia within 30 days of starting placebo. Not ITT analysis, and the missing participants' data described was clearly of importance to the analysis
Selective reporting (reporting bias)	Low risk	All pre-specified and expected outcomes were reported
Other bias	Low risk	Study appeared to be free of other sources of bias

Van-Holten 1987

Methods	Randomised, non-placebo-controlled study
Participants	N = 161 Women with BCBM
Interventions	Indefinite oral pamidronate 150 mg twice/d or open control Initial pamidronate dose was 300 mg twice/d from July 1983-February 1985 (N = 48 on pamidronate) but because of gastrointestinal toxicity, was reduced to 150 mg twice/d for the remainder of study until March 1988 (final participant enrolled)
Outcomes	Morbidity to bone: hypercalcaemia, severe bone pain needing radiotherapy or surgery, pathological or imminent fractures, event-free survival, QoL
Notes	Final analysis of data was first presented in Van Holten-Verzantvoort 1987. QoL was reported separately in 144 participants (Van Holten-Verzantvoort 1991). Analysis by ITT. Those receiving high-dose pamidronate were not included in the analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomised performed separately per participating centre" (14)
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study

Van-Holten 1987 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Bone scans and radiographs were reviewed by an independent experienced radiologist ...for skeletal disease progression, stabilisation or remission according to the World Health Organization (WHO) criteria. The reviewer was blinded for the supportive treatment given (pamidronate or control)."..."Two of the 14 participating centers could not make radiologic examinations available to central review" (pg.493)
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis. Only 2 participants in the pamidronate group were lost to follow-up
Selective reporting (reporting bias)	Low risk	All endpoints were reported
Other bias	Low risk	Study appeared to be free of other sources of bias

Van-Holten 1996

Methods	Randomised, multi-centre, open, controlled study
Participants	N = 124 Women with BC with either established extra-skeletal metastases or locally advanced disease but no bone metastases
Interventions	Indefinite pamidronate 150 mg orally twice/d or open control. 6 participants received 300 mg twice/d and were included in the ITT analysis Anti-tumour therapy was freely allowed
Outcomes	Skeletal morbidity: hypercalcaemia, severe bone pain needing radiotherapy or surgery, pathological fracture, change in systemic therapy for bone metastases, QoL; event-free period
Notes	ITT analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned per participation centre" (9)
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Consecutive investigations were reviewed for the first development of bone metastases by two expert readers blinded for clinical data" (p. 451)
Incomplete outcome data (attrition bias)	Unclear risk	ITT analysis. Early withdrawal of participants in the pamidronate group (15/65) only due to gastro-intestinal complaints; an additional 19/65 participants in

Van-Holten 1996 *(Continued)*

All outcomes		the pamidronate group (29.2%) and 5/59 (18.5%) in the control group withdrew due to reported reasons
Selective reporting (reporting bias)	Low risk	All endpoints were reported
Other bias	Low risk	Study appeared to be free of other sources of bias

von Au 2016

Methods	Phase III prospective, randomised, open-label, non-inferiority trial, 1995-1999
Participants	N = 321 Women with confirmed bone metastases from BC > 18 years with ≥1 bone metastasis, histologically confirmed BC, ECOG performance status of 0–2, approximate life expectancy of > 6 months
Interventions	375 randomly assigned to 1/3 treatment groups: 60 mg pamidronate intravenously every 3 weeks (N = 129) 900 mg clodronate intravenously every 3 weeks (N = 120) 2400 mg oral clodronate daily (n = 126)
Outcomes	Primary: "compare the side effects of oral versus intravenous BP treatment " Secondary: "assess their clinical effectiveness."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Assessments were performed at baseline and every 3 months thereafter. Outcomes assessed included adverse events, participant compliance, pain development and occurrence of pathologic fractures. Given the number of self-reported outcomes and no information about assessment of pathologic fractures, we assessed this study to be potentially at high risk of bias
Incomplete outcome data (attrition bias) All outcomes	High risk	High dropout rate, 14% (54/375 randomised); unclear if differential between arms; unclear flow diagram

von Au 2016 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Median follow-up 15 months; but recruitment completed in 1999, publication delayed 17 years to 2016 Trial not registered
Other bias	Low risk	Study appeared to be free of other sources of bias

Z-FAST 2012

Methods	Z-FAST 2012, one of the triplet adjuvant zoledronic acid studies. Participants were from 94 US and Canadian community-based centres. Open-label, randomised, placebo-controlled study
Participants	N = 602 Postmenopausal women with early-stage (surgically resectable stage I, II, or IIIa) ER and/or PR–positive BC as well as baseline LS and TH T scores of ≥ 2.0, who were on adjuvant letrozole 2.5 mg orally every day for 5 years Baseline characteristics: similar between groups. Median age 60 years in both arms; all participants hormone receptor-positive; no information on stages or characteristics of BC; no adjuvant chemotherapy (54.3% upfront group, 51.7% delayed group) (Coleman 2009)
Interventions	Upfront zoledronic acid 4 mg every 6 months (after randomisation) or delayed start zoledronic acid (defined by post-baseline LS or TH T score decreased to < –2.0; any clinical, non-traumatic fracture occurred; or asymptomatic vertebral fracture identified at 36 months) for 5 years
Outcomes	Primary endpoint: difference in percentage change in LS BMD from baseline to 12 months Secondary endpoints: percentage change difference in LS BMD from baseline to 24, 36, and 60 months; percentage change difference in TH BMD from baseline to 12, 24, 36 and 60 months; percentage change differences in serum N-telopeptide and serum bone-specific alkaline phosphatase concentrations from baseline to 12, 24, 36 and 60 months; fracture incidence at 36 months; time-to-disease recurrence, and rate of decrease in LS and TH BMD during the study. OS or death was not a pre-specified endpoint
Notes	Statistics: This was predominantly a BMD study with disease recurrence as one of its pre-specified endpoints. However, the study authors reported that "the study was not powered to detect a difference in the incidence of clinical fractures or BC relapse" Z-FAST 2012. Sites of recurrences reported ITT analysis. Follow-up was 61 months (Coleman 2009)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Random assignment". Baseline characteristics were similar between groups; randomisation appeared to be achieved
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias)	Unclear risk	Central reader (BioImaging Technologies Inc, Newtown, PA) analysed all DEXA scans for the efficacy analysis

Z-FAST 2012 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis. 301 participants in each group. 300 in ITT population: "1 patient erroneously randomised in each group"
Selective reporting (reporting bias)	Low risk	All pre-specified and expected outcomes were reported
Other bias	Low risk	Study appeared to be free of other sources of bias

ZICE 2014

Methods	Phase III, open-label, randomised, controlled non-inferiority trial. UK trial, 99 centres
Participants	N = 1404 Women ≥ 18 years with metastatic BC and ≥ 1 documented bone lesion, performance status ECOG 0-2
Interventions	Oral ibandronate 50 mg/d continuous vs zoledronate 4 mg every 3-4 weeks, for 96 weeks
Outcomes	Primary outcome: SRE Secondary outcomes: time to first SRE, proportion of participants with SRE, OS, pain, QoL, toxicity, health resource usage
Notes	Per-protocol analysis included 654 participants in the ibandronic-acid group and 672 in the zoledronic-acid group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomly assigned (1:1 ratio) ... by use of a computer-generated randomisation list at the Wales Cancer Trials Unit (WCTU). Randomisation was stratified, within blocks of size four, according to whether the patient was currently receiving chemotherapy, hormone therapy, or had had a previous skeletal-related event within the last 3 months or had planned radiotherapy."
Allocation concealment (selection bias)	Low risk	"Research nurses (who recruited the patients) telephoning the WCTU, where randomisation and treatment allocation was done by a trial/data manager interacting with a computerised system. "
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding of outcome assessors mentioned. The primary endpoint for non-inferiority was frequency and timing of SREs. A SRE was a composite event defined as one of: requirement for orthopaedic surgery, vertebroplasty, or radiotherapy to bone; symptomatic vertebral fracture; pathological non-vertebral fracture; spinal-cord compression; and hypercalcaemia of malignancy

ZICE 2014 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	High levels of attrition in both arms (withdrawal, treatment discontinuation, death), but comprehensively documented and balanced between arms. ITT analysis
Selective reporting (reporting bias)	Low risk	All primary and secondary endpoints presented
Other bias	Low risk	Study appears to be free of other sources of bias

ZO-FAST 2013

Methods	Open-label, multicentre, randomised 1:1, phase III study. 132 centres in 28 countries (Europe, Asia-Pacific, Middle East, Latin America)
Participants	N = 1065 Postmenopausal women with early-stage (surgically resectable stage I-IIIA) ER- and/or PR–positive BC, baseline LS and TH T scores ≥ 2.0, on adjuvant letrozole 2.5 mg daily for 5 years Baseline: median age 57; 78% white, performance status ECOG 0 (89%), 1 (10%); stage I (60%), II-III (40%); primary tumour: < T2 (60%), ≥ T2 (40%); axillary nodal status: negative (43%), positive (57%); adjuvant chemotherapy: no (46%), yes (54%)
Interventions	Immediate: zoledronic acid iv 4 mg every 6 months (< 4 weeks from randomisation) vs Delayed: zoledronic acid iv 4 mg every 6 months started at post-baseline LS or TH T score decreased to < –2.0; any clinical, nontraumatic fracture occurred; or asymptomatic vertebral fracture
Outcomes	Primary endpoint: percentage change in LS BMD at 12 months Secondary endpoints: "percentage change difference in TH BMD from baseline to each assessment, 3-year fracture incidence, time to disease recurrence (local relapse or distant metastasis), OS, and safety"
Notes	Predominantly a BMD study designed and powered to study "the effect of immediate and delayed treatment on change in BMD." Final efficacy analysis at 60 months

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned". Baseline characteristics were similar between groups; randomisation appeared to be achieved
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information about blinding of outcome assessment

ZO-FAST 2013 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis. Recurrence data complete. However BMD data incomplete at 36 months: only 314/434 participants on early-treatment group and 319/434 on the delayed-treatment group had both baseline and 36-month BMD data
Selective reporting (reporting bias)	Low risk	All pre-specified and expected outcomes reported
Other bias	Low risk	A sensitivity analysis censoring delayed-treatment group at the first dose of zoledronic acid was also performed so to preclude the time difference of treatment as a confounding factor. The results before and after censoring were similar

ZOOM 2013

Methods	Open-label, non-inferiority, phase 3 randomised 1:1 trial. Conducted in 62 Italian centres
Participants	N = 425 Women > 18 years with metastatic BC and ≥ 1 radiologically documented bone metastasis, having completed 12-15 months of iv zoledronic acid every 3-4 weeks
Interventions	4 mg iv zoledronic acid every 4 weeks for 12 months (N = 205) or 4 mg iv zoledronic acid every 12 weeks for 12 months (N = 216) All participants received daily calcium (500 mg) and vitamin D (400-500 IU)
Outcomes	Primary endpoint: skeletal morbidity rate (SREs per participant per year) Secondary endpoints: incidence of each SRE per year, proportion of participants who had SREs, time to first SRE, bone pain, use of analgesics, N-telopeptide of type I collagen concentration, and safety
Notes	SRE rate for control group anticipated to be 0.91 events per participants per year. Pre-defined non-inferiority HR 0.67 (SRE rate 0.56), 420 participants needed to detect non-inferiority with 80% power (one-sided α = 0·025) Actual control rate was lower at 0.26 events per participant per year, but observed pooled standard deviation of study was 1/3 that estimated in power calculations. To maintain study power, "non-inferiority margin was reduced, according to the ratio of the two estimated SDs, to 0·19."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Random list generated by an independent statistician through a validated computer programme"
Allocation concealment (selection bias)	Low risk	"Allocated by the investigator to the smallest available random number of the list ... Sealed envelopes containing the randomisation code for each patient were produced and sent to centres: the investigators opened them sequentially when assigning a new patient"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label

ZOOM 2013 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Nobody involved in the study was masked to treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 149/209 (71.3%) in every-12-weeks intervention group and 142/216 (65.7%) in every-4-weeks control group completed the 12-month study period. Analysed by ITT
Selective reporting (reporting bias)	Low risk	All primary and secondary outcomes reported
Other bias	Low risk	Study appeared to be free of other sources of bias

ABC: advanced breast cancer
AE: adverse event
BC: breast cancer
BCBM: breast cancer with bone metastases
BMD: bone mineral density
BMFS: bone metastasis-free survival
CK: anti-pan-cytokeratine (CK) antibody
CT: computed tomography
CTR: control
DFS: disease-free survival
DMB: denosumab
DTC: detectable tumour cells
EBC: early breast cancer
ECOG: Eastern cooperative oncology group
ER: oestrogen receptor
G-CSF: granulocyte colony-stimulating factor
HR: hazard ratio
im: intramuscular
ITT: intention-to-treat
iv.: intravenous
LS: lumbar spine
MRI: magnetic resonance imaging
ONJ: osteonecrosis of the jaw
PgR: progesterone receptor
RFS: recurrence-free survival
OS: overall survival
QoL: quality of life
sc: subcutaneous
SRE: skeletal-related event
sCTx: serum C-Telopeptide
TH: total hip
uNTx: urinary N-telopeptide

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
ANZAC 2013	Evaluated short-term anti-tumour effects of neoadjuvant chemotherapy plus or minus zoledronate in women with invasive breast cancer, evaluating biological endpoints including apoptosis, proliferation and angiogenesis
Berenson 2001	Study population was made up of patients with myeloma and breast cancer. Results were not stratified according to disease. Data for breast cancer were requested but not received

Study	Reason for exclusion
Delmas 1997	The study was a BMD trial with no specific information about recurrence or death other than this: "There were two deaths due to recurrence of breast cancer, one in each group." It did not mention the types of recurrence for these patients, overall recurrence or overall survival. For the endpoint of meta-analysis which specifically addressed locoregional/bone/visceral metastases and death, this information was not specific enough to be incorporated in the meta-analysis
Fuleihan 2005	Inadequate randomisation and allocation concealment in this adjuvant pamidronate trial (initial assignment made after coin toss by clinical nurse, alternating assignment of participants thereafter)
Greenspan 2008	BMD study for EBC (risedronate 35 mg orally, weekly or placebo). Recurrence mentioned briefly to be no different between treatment arms, but absolute numbers were not reported, nor did the manuscript expand on this in results or discussion section. Data for recurrence was requested but not received
Hines 2009	A BMD study randomising women to risedronate or placebo for 1 year but no SRE endpoints were discussed
Jagdev 2001	This was a small randomised study (N = 51) with a mixed study population, although breast cancer patients were included. However, outcomes were reported for the whole population only
Kokufu 2010	This Japanese adjuvant pamidronate study was a non-randomised study with treatment assignment based on patient preference
Leppa 2005	Study report from Saarto 2004 study examining the impact of adjuvant clodronate on survival outcomes, stratified by postoperative baseline matrix metalloproteinase - 2 levels (low, high). Participants were stratified by MMP-2 status and the effect of oral clodronate was compared on both groups. The mortality data from the combined cohort (Saarto 2004) was reported in Pavlakis 2005 update
Mathevet 2016 (NEOZOL)	Randomised phase II trial of neoadjuvant trial of zoledronate vs placebo; it did not include DFS or OS endpoints
McCloskey 2009	A subset of patients with biomarker and BMD measured in Powles 2006 (851/1069) were reported in an analysis that correlated BMD, bone turnover markers and bone metastases. However, the bone metastases incidence of the ITT population was not reported
ProBONE II 2015	Randomised phase II study, BMD endpoints only Methods: changes in BMD and trabecular bone score were assessed in 70 participants who were recruited in the double-blind, placebo-controlled ProBONE-II trial and randomised to receive either zoledronate (N = 34) or placebo (N = 36) for 2 years. The changes were assessed at baseline and at 12 and 24 months after treatment initiation
Saarto 2005	Histological study describing the effect of adjuvant clodronate on bone biopsies obtained from a small subset (N = 63) of consenting participants within included adjuvant study by Saarto 2004 (N = 299). No additional clinical outcomes were reported
Scotti 2014 (BONADIUV)	BMD, safety & tolerability endpoints only Single-blind, randomised, placebo-controlled phase II study designed to evaluate the impact of oral ibandronate (150 mg monthly) on BMD in osteopenic women on AIs in adjuvant setting
Sestak 2014 (IBIS-II)	Bone substudy of IBIS-II primary prevention trial of anastrozole. Primary endpoint BMD. The double-blind IBIS-II trial recruited 3864 healthy, postmenopausal women at increased risk of breast cancer and randomly allocated them oral anastrozole or placebo. 1410 (36%) postmenopausal women were then enrolled in a bone substudy and stratified at baseline according to their lowest baseline T score at spine or femoral neck (stratum I: T score ≥ -1.0; stratum II: T score ≥ -2.5 but I<

Study	Reason for exclusion
	-1.0; stratum III: T score < -2.5 but > -4.0). Women in stratum I were monitored only; women in stratum III were all given risedronate (35 mg/week). Women in stratum II were randomly assigned (1:1) to risedronate (35 mg/week) or placebo
Siris 1983	Primary endpoints were biochemical: urinary calcium, hydroxyproline, serum calcium. Effect on bone pain was reported but only in a qualitative fashion
Vehmanen 2001	No SRE outcomes were reported. Effect of clodronate on BMD only
Vehmanen 2004	No SRE outcomes were reported. Effect of clodronate on BMD only
Weinfurt 2004	Detailed QoL analysis in a whole breast cancer patient population within the including zoledronate versus pamidronate study by Rosen 2004. No additional comparative data were provided between the treatment arms

BMD: bone mineral density
EBC: early breast cancer
ITT: intention-to-treat
QoL: quality of life
SRE: skeletal-related event

Characteristics of studies awaiting assessment *[ordered by study ID]*

BISMARK 2012

Methods	Randomised, open-label study
Participants	Women with advanced breast cancer and radiographically confirmed bone metastases
Interventions	Standard schedule: zoledronic acid iv over 15 min once every 3-4 weeks for 24 months Bone marker-directed schedule: zoledronic acid iv over 15 min once every 3-4, 8-9 or 15-16 weeks (based on serum N-telopeptide: creatinine ratio) for 24 months
Outcomes	Primary outcomes: fractures, radiotherapy to bone, hypercalcaemia, orthopedic surgery and spinal cord compression Secondary outcomes: quality of life, clinical burden of skeletal complications, pain, performance status and analgesic use, incidence of new bone metastases, overall survival, bisphosphonate use and expenditure on administration, health care utilisation and clinical utility of the "point of care" test for N-telopeptides (NTx) excretion
Notes	Study start date: March 2006. Estimated enrolment: 1500

Characteristics of ongoing studies *[ordered by study ID]*

Amir 2013

Trial name or title	Randomized feasibility study of de-escalated (every 12 weeks) versus standard (every 3 to 4 weeks) intravenous pamidronate in women with low-risk bone metastases from breast cancer
Methods	Pilot, randomised phase II, non-inferiority trial
Participants	Patients receiving intravenous bisphosphonates for ≥ 3 months and with low-risk baseline serum C-telopeptide (CTx) levels (< 600 ng/L)

Amir 2013 *(Continued)*

Interventions	Control: 90 mg pamidronate iv every 3-4 weeks Intervention (de-escalated): 90 mg pamidronate iv every 12 weeks
Outcomes	CTx, bone alkaline phosphatase, and pain scores (Brief Pain Inventory and Functional Assessment of Cancer Therapy-Bone Pain) were collected every 12 weeks for 48 weeks
Starting date	
Contact information	E. Amir, Division of Medical Oncology and Hematology, University of Toronto, Princess Margaret Hospital, Toronto ON, M5G 2M9, Canada
Notes	

D-CARE 2011

Trial name or title	Study of denosumab as adjuvant treatment for women with high risk early breast cancer receiving neoadjuvant or adjuvant therapy
Methods	Randomised phase III, double-blind, placebo-controlled trial
Participants	Patients with EBC
Interventions	Denosumab sc 120 mg 6-monthly or placebo for 5 years. All participants take oral calcium and vitamin D for 5 years
Outcomes	Primary endpoint: bone metastases-free survival Secondary endpoints: DFS, OS, distant RFS, safety
Starting date	2010
Contact information	ClinicalTrials.gov identifier: NCT01077154. Amgen Call Center: 866-572-6436
Notes	International multi-centre trial. Estimated enrolment to be completed by October 2016 with 4500 participants

El-Ibrashi 2016

Trial name or title	Zoledronic acid combined with adjuvant tamoxifen with or without ovarian function suppression in premenopausal early breast cancer patients
Methods	Premenopausal females who had undergone primary surgery for stage I, II ER-positive and/or PR-positive BC with < 10 positive lymph nodes. All participants were scheduled for standard tamoxifen 20 mg/d for five years plus goserelin 3.6 mg every 28 days
Participants	Premenopausal EBC patients (n = 300), median follow up 98.4 months (range 14-120)
Interventions	Randomised to zoledronic acid 4 mg every 6 months for 3 years (group A) and without zoledronic acid (group B)
Outcomes	Primary: toxicity and DFS

El-Ibrashi 2016 *(Continued)*

	Secondary: OS
Starting date	April 2005-March 2012
Contact information	
Notes	SABCS Dec 2015: Abstract P5-15-04 "Adding ZOL [zoledronic acid] to endocrine therapy strongly suggests improved DFS versus endocrine therapy alone (90% versus 85% for an absolute increase of 5%). There were fewer disease recurrences in the ZOL group versus no ZOL group (12% vs. 16%) with the greatest reductions in the loco-regional recurrence (3% vs. 5%), distant metastasis (6% vs. 7%) and bone metastasis (3% vs. 5%). Conclusion: ZOL with adjuvant endocrine therapy were generally well tolerated with no reports of renal failure or osteonecrosis of the jaw. So, a twice yearly ZOL enhanced the efficacy of adjuvant endocrine treatment, and this benefit is maintained for long time" We contacted study authors unpublished data

Fallowfield 2015

Trial name or title	The impact of skeletal-related events on pain interference in patients with advanced breast cancer and bone metastases
Methods	Randomised, double-blind, double-dummy, placebo-controlled trial
Participants	Advanced BC and bone metastases
Interventions	Randomised 1:1 to receive monthly denosumab 120 mg sc or zoledronic acid 4 mg iv, (adjusted for renal function)
Outcomes	Primary: the impact of SREs on pain interference in patients with BCBM
Starting date	
Contact information	Lesley Fallowfield: L.J.Fallowfield@sussex.ac.uk
Notes	

FEMZONE 2014

Trial name or title	FemZone trial: a randomized phase II trial comparing neoadjuvant letrozole and zoledronic acid with letrozole in primary breast cancer patients
Methods	Prospective randomised phase II trial
Participants	Randomly assigned to receive either LET 2.5 mg/d (N = 79) or the combination of LET 2.5 mg/d and a total of 7 infusions of zoledronic acid 4 mg every 4 weeks (N = 89) for 6 months. Primary endpoint was clinical response rate as assessed by mammogram readings. The study was terminated prematurely due to insufficient recruitment.
Interventions	Randomly assigned to receive either LET 2.5 mg/d (N = 79) or the combination of LET 2.5 mg/d and a total of 7 infusions of zoledronic acid 4 mg every 4 weeks (N = 89) for 6 months
Outcomes	Primary endpoint was clinical response rate as assessed by mammogram readings

FEMZONE 2014 *(Continued)*

Starting date	Terminated early because of poor recruitment. Exploratory analysis reported at this stage
Contact information	Peter A Fasching: ed.negnalre-ku@gnihcsaf.retep
Notes	EUDRA CT: EUCTR2004-004007-37-DE

HOBOE 2013

Trial name or title	A study of hormonal adjuvant treatment effect on bone mineral density in early breast cancer patients
Methods	Randomised, controlled, phase III (open-label), 3-arm
Participants	Any BC with M0 disease, post-surgery with indication of adjuvant hormone therapy
Interventions	Arm A: tamoxifen 20 mg/d and/or triptorelin 3.75 mg every month (for pre-menopausal women) for 5 years, or arm B: letrozole 2.5 mg/d and/or triptorelin 3.75 mg every month (for pre-menopausal women) for 5 years or arm C (experimental): letrozole 2.5 mg/d and/or triptorelin 3.75 mg every month (for pre-menopausal women) and zoledronic acid every 6 months for 5 years
Outcomes	Primary outcomes: BMD (at 12 months), DSF in pre-menopausal participants Secondary outcomes: BMD yearly, DSF in post-menopausal participants, OS, toxicity, biomarker
Starting date	March 2004
Contact information	ClinicalTrials.gov identifier: NCT00412022. Andrea De Matteis, Giuseppe D'Aiuto, Francesco Perrone, National Cancer Institute, Naples
Notes	Italian study. Enrolment (450/1271) expected completion March 2013

Jacobs 2014 (ODYSSEY)

Trial name or title	ODYSSEY
Methods	Randomised, double-blind, phase IV study (post-marketing)
Participants	BC patients with high-risk bone metastases (prior SRE, bone progression, bone pain or levels of bone turnover marker serum C-telopeptide (sCTX) > 400 ng/L) despite > 3 months of pamidronate (PAM) use
Interventions	Randomised in a double-blind manner to either switch to zoledronate (ZA) or continue on PAM every 4 weeks for 12 weeks
Outcomes	Primary outcome: proportion of participants achieving a fall in sCTX at 12 weeks Secondary outcomes were pain control (Brief Pain Inventory and FACT-BP) and toxicity
Starting date	Aug 2012
Contact information	PI: Dr Mark Clemons, The Ottawa Hospital
Notes	Clinicaltrials.gov: NCT01907880

Jiang 2016

Trial name or title	Efficacy and safety of denosumab from a phase III, randomized, active-controlled study compared with zoledronic acid in patients of Asian ancestry with bone metastases from solid tumours
Methods	Phase III, double-blind, denosumab (DmAb) vs zoledronic acid (ZA)
Participants	"Patients >18 years who had a confirmed solid tumor, evidence of 1 bone metastasis and ECOG score 0-2 were enrolled." "485 (DmAb = 326, ZA = 159) patients were randomized; 90% of patients had either completed the study or withdrawn by planned data cut-off (29 February 2016). Mean (SD) age of patients was 53.9 (11.38) years; 67% patients were women, 93% Chinese, 50% had BC and 27% had non-small cell lung cancer."
Interventions	Methods: "Randomized (2:1) to receive either DmAb 120 mg subcutaneously every 4 weeks (Q4W) or ZA 4 mg intravenously Q4W for 49 weeks and are being followed up to Wk 73."
Outcomes	Primary: markers of bone turnover (% change in uNTx/uCr) from baseline to 13 weeks Secondary: changes in bone-specific ALP; first on-study SRE
Starting date	
Contact information	Not specified
Notes	Results: the mean change in uNTx/uCr from baseline to Wk 13 was -81.9% for DmAb and -75.2% for ZA (ANCOVA; P < 0.0001). The median change in S-BALP from baseline to week 13 was -36.8% (DmAb) and -30.3% (ZA) (P = 0.027). Rate of developing any on-study SRE within the first year after initialising treatment was lower in participants receiving DmAb vs ZA (4.9% vs 6.3%) without statistical significance. Incidence of AEs was similar in DmAb and ZA groups (89% vs 91%), with most common AEs being anaemia (25% vs 24%), white blood cell count decreased (21% vs 24%), and pyrexia (13% vs 21%); overall incidence of serious AEs: 14% vs 9%. One serious AE (muscular weakness) was reported as related to study treatment. Conclusions: DmAb was found to be superior than ZA in reducing uNTx/uCr overall and Chinese patients. No new safety concerns were identified with DmAb

JONIE-1 2013

Trial name or title	Disease-free survival and Ki67 analysis of a randomized controlled trial comparing zoledronic acid plus chemotherapy with chemotherapy alone as a neoadjuvant treatment in patients with HER2-negative primary breast cancer
Methods	Addition of zoledronate to neoadjuvant chemotherapy
Participants	Women with stage IIA-IIIB HER-2-negative BC
Interventions	Experimental: CTZ group - chemotherapy (3 x FEC, 12 x weekly paclitaxel) followed by zoledronic acid Control: CT group - chemotherapy only (3 x FEC, 12 x weekly paclitaxel)
Outcomes	DFS Pathologic complete response (pCR) rates between baseline Ki67 high (20% and > 20%) with Ki67 low (< 20%) in ER-positive cohort

JONIE-1 2013 *(Continued)*

Starting date	N = 188 participants accrued between March 2010-April 2012
Contact information	
Notes	Miura D et al. SABCS 2013. [PD3-7]

Kummel 2016 (GeparX)

Trial name or title	Investigating denosumab as add-on neoadjuvant treatment for hormone receptor-negative, RANK-positive or RANK-negative primary breast cancer and two different nab-Paclitaxel schedules-2x2 factorial design
Methods	"Denosumab will be tested in patients with HR- primary breast cancer in addition to neoadjuvant chemotherapy (NACT)" Methods: GeparX will randomise 778 patients to NACT +/- denosumab (120 mg sc every 4 weeks for 6 cycles), stratified by lymphocyte predominant BC (< 50% vs > 50% stromal tumor infiltrating lymphocytes [TILs]), HER2 status, and epirubicin/cyclophosphamide (EC, every 2 weeks vs every 3 weeks). Secondarily participants will be randomised to the backbone treatment of nab-paclitaxel (nP) 125 mg/m^2 weekly + EC or nP 125 mg/m^2 day 1 and 8 every 22 days + EC, stratified by the first randomisation. Carboplatin will be given in triple negative (TNBC) and trastuzumab + pertuzumab in HER2+ BC
Participants	Patients with primary cT1c-cT4a-d BC, centrally confirmed HR- and centrally assessed HER2, Ki-67, TIL and RANK status on core biopsy can be enrolled
Interventions	NACT +/- denosumab (120 mg sc every 4 weeks for 6 cycles)
Outcomes	Primary: pCR (ypT0 ypN0) rates of NACT +/- Dmab Secondary: interaction of denosumab treatment with RANK expression; pCR rates per arm for both randomisations in TNBC and HER2+ BC; pCR rates in RANK high vs low; other pCR definitions for both randomisations; response rates; breast conservation rates; toxicity and compliance; and survival
Starting date	April 2016
Contact information	Contact: Sherko Kümmel, MD ++49 201 174 ext 33003 s.kuemmel@kliniken-essen-mitte.de
Notes	NCT02682693

NCT00196895

Trial name or title	Study in elderly patients with early breast cancer
Methods	Randomised, phase III, (open-label)
Participants	Node-positive BC after surgery, ≥ 65 years
Interventions	Oral ibandronate 50 mg daily/ iv ibandronate 6 mg every 4 weeks for 2 years; or Oral ibandronate 50 mg daily/ im ibandronate 6 mg every 4 weeks for 2 years and capecitabine 2000 mg/m^2 day 1-14 every 22 days x 6 cycles
Outcomes	Primary endpoint: any relapse Secondary endpoints: OS, premature discontinuation, completed months of ibandronate, change of preference of ibandronate application, osteoporosis, toxicity, QoL (EORTC Q30)
Starting date	June 2004
Contact information	ClinicalTrials.gov identifier: NCT00196859. Horst Mochnatzki, Birgit Raasch
Notes	German study. Estimated enrolment completed by October 2010 with 1500 patients

NCT00301886

Trial name or title	Zoledronate or ibandronate in preventing bone problems in women with stage IV breast cancer that has spread to the bone
Methods	Randomised, controlled, phase III trial (open-label)
Participants	Stage IV BCBM
Interventions	Oral ibandronate day 1-28 or zoledronate every 28 days for up to 18 courses
Outcomes	Primary endpoint: SRE Secondary endpoints: time to SRE, pain score, performance status, toxicity
Starting date	May 2006
Contact information	ClinicalTrials.gov identifier: NCT00301886. Saul Rivkin, Swedish Cancer Institute at Swedish Medical Center - First Hill Campus
Notes	Enrolment completed (N = 466), awaiting results

NCT00524849

Trial name or title	Zometa and circulating vascular endothelial growth factor (VEGF) in breast cancer patients with bone metastasis
Methods	Randomised, controlled, phase III trial (open-label)
Participants	BCBM

NCT00524849 *(Continued)*

Interventions	Zoledronate 4 mg every 4 weeks or zoledronic acid 1 mg weekly
Outcomes	Primary endpoint: circulating vascular endothelial growth factor levels Secondary endpoints: time to first SRE, time to bone progression disease, progression-free survival, OS
Starting date	November 2006
Contact information	ClinicalTrials.gov identifier: NCT00524849. Xichun Hu, Fudan University Cancer Hospital
Notes	Chinese Trial. Enrolment completed January 2010 (N = 60), awaiting results

NCT01129336

Trial name or title	Effect of zoledronic acid as anti-cancer treatment in metastatic breast cancer patients
Methods	Randomised, controlled, phase IV (open-label), 3 arms
Participants	BCBM
Interventions	Arm A: zoledronate (months 1-6) for participants with no bone metastases; or Arm B: zoledronate (months 7-12) for participants with no bone metastases; or Arm C: zoledronate (months 1 to 18) for participants with bone metastases
Outcomes	Primary endpoint: progression-free survival Secondary endpoints: proportion of circulating tumour cells, time to disease progression, biomarker, functional assessment
Starting date	May 2010
Contact information	ClinicalTrials.gov identifier: NCT01129336. Novartis pharmaceutical
Notes	US study. Estimated enrolment to be completed by November 2012 for 280 participants

NEOZOTAC

Trial name or title	Phase III randomized trial with neoadjuvant chemotherapy (TAC) with or without zoledronic acid for patients with HER2-negative large resectable or stage II or III breast cancer (BC)—A Dutch Breast Cancer Trialists' Group (BOOG) study
Methods	National, multicenter, randomised study
Participants	Stage II/III, measurable, HER2-negative BC and absence of prior bisphosphonate usage
Interventions	Comparing the efficacy of TAC (docetaxel, Adriamycin and cyclophosphamide iv) CT followed by G-CSF on day 2 with or without zoledronic acid 4 mg im, every 3 weeks
Outcomes	Primary: pCR rate
Starting date	April 2010

NEOZOTAC *(Continued)*

Contact information	Judith Kroep, MD and NCT01099436
Notes	

SAKK 96/12 2014

Trial name or title	Prevention of symptomatic skeletal events with denosumab administered every 4 weeks versus every 12 weeks: a non-inferiority phase III trial
Methods	Open-label, randomised, phase III non-inferiority trial
Participants	Patients with breast or prostate cancer with bone metastases and adequate organ function are eligible. This trial is open for international collaboration
Interventions	Denosumab 12 0mg every 12 weeks versus 120 mg every 4 weeks
Outcomes	Primary endpoint: time to first on-trial symptomatic skeletal events (SSE; clinically significant pathological fracture, radiation therapy to bone, surgery to bone or spinal cord compression) Secondary endpoints: safety, time to subsequent on-trial SSE, QoL, health economic outcomes, and change in bone turnover markers
Starting date	July 2014
Contact information	Andrea Fuhrer - andrea.fuhrer@sakk.ch
Notes	Templeton 2014

SUCCESS 2013

Trial name or title	Multi-centre prospective randomised phase III study to the comparison of FEC docetaxel chemotherapy versus FEC docetaxel-gemcitabine chemotherapy, as well as 2 versus 5 years of zoledronate therapy in the adjuvant therapy of patients with breast cancer
Methods	Randomised controlled trial (2 x 2 factorial design)
Participants	Stage I-IIIa (pT1-4, N1-3, M0 or high risk pN0)
Interventions	Randomised to 3 cycles of epirubicin-fluorouracil-cyclophosphamide followed by 3 cycles docetaxel (FEC-D), then endocrine therapy + zoledronic acid 2 years or 5 years; or randomised to 3 cycles of FEC followed by 3 cycles of gemcitabine-docetaxel (DG), then endocrine therapy + zoledronic acid 2 years or 5 years
Outcomes	Primary endpoint: time to recurrence Secondary endpoints: distant DSF, OS, QoL, SREs, safety, prognostic and predictive value of minimal residual disease
Starting date	June 2005
Contact information	Reference URL www.success-studie.de/a/study.htm. Professor W. Janni, Medical Center of the Heine's University of Dusseldorf

SUCCESS 2013 *(Continued)*

Notes	German study. Enrolment completed March 2007 (N = 3754), awaiting results

TRIUMPH 2012

Trial name or title	A phase II, multicenter trial evaluating the efficacy of de-escalated bisphosphonate therapy in metastatic breast cancer patients at low-risk of skeletal-related events
Methods	
Participants	Women with BC and radiologic, scintigraphic- and/or biopsy-confirmed bone metastases who had received ≥ 3 months of 3–4 weekly iv pamidronate
Interventions	All study participants were switched from 3–4-weekly to 12-weekly pamidronate
Outcomes	Exploratory biomarkers, pain, any SREs
Starting date	October 2010
Contact information	Addison CL. Registered with Ontario Cancer Trials (October 2013) and www.canadiancancertrials.ca (10-047)
Notes	Addison 2014

AE: adverse events
BC: breast cancer
BCBM: breast cancer with bone metastasis
BMD: bone mineral density
CT: chemotherapywww.success-studie.de/a/study.htm
DFS: disease-free survival
EBC: early breast cancer
ER: oestrogen receptor
FEC: fluorouracil, epirubicin, cyclophosphamide
iv: intravenous
M0: no clinical or radiographic evidence of distant metastases
OS: overall survival
pN0: no regional lymph node metastasis identified histologically
QoL: quality of life
RFS: recurrence-free survival
SABCS: San Antonio Breast Cancer Symposium
SRE: skeletal-related event
sc: subcutaneous

DATA AND ANALYSES

Comparison 1. Early Breast Cancer (EBC)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Bone metastases	14		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Bisphosphonate vs control	11	15005	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.75, 0.99]
1.2 Immediate vs delayed	3	2190	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.38, 1.19]
2 Bone metastases by bisphosphonate	14	17195	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.74, 0.97]
2.1 Zoledronate 4 mg iv every 4 weeks	8	8267	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.60, 0.99]
2.2 Clodronate 1600 mg oral daily	4	4981	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.70, 1.00]
2.3 Pamidronate 150 mg oral twice a day	1	953	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.88, 1.50]
2.4 Ibandronate 50 mg oral daily	1	2994	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.56, 1.13]
3 Visceral recurrence	13	17092	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.91, 1.17]
3.1 Bisphosphonate vs control	10	14902	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.92, 1.18]
3.2 Immediate vs delayed	3	2190	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.46, 1.60]
4 Locoregional recurrence	11	15721	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.83, 1.19]
4.1 Bisphosphonate vs control	8	13531	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.85, 1.20]
4.2 Immediate vs delayed	3	2190	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.26, 4.48]
5 Overall recurrence	14	17196	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.88, 1.11]
5.1 Bisphosphonate vs control	11	15005	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.89, 1.13]
5.2 Immediate vs delayed	3	2191	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.52, 1.46]
6 Overall recurrence by bisphosphonate	14	17196	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.88, 1.11]
6.1 Zoledronate 4 mg iv every 4 weeks	8	8268	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.76, 1.23]

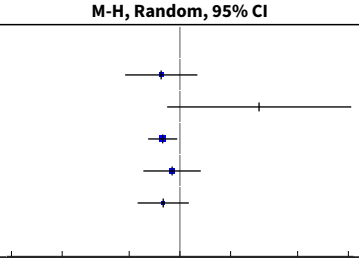
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.2 Clodronate 1600 mg oral daily	4	4981	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.84, 1.19]
6.3 Pamidronate 150 mg oral twice a day	1	953	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.94, 1.24]
6.4 Ibandronate 50 mg oral daily	1	2994	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.82, 1.22]
7 Overall survival: time-to-event outcome	10	15013	Hazard Ratio (Fixed, 95% CI)	0.90 [0.82, 0.98]
7.1 Bisphosphonate vs control	9	13949	Hazard Ratio (Fixed, 95% CI)	0.91 [0.83, 0.99]
7.2 Immediate vs delayed bisphosphonate	1	1064	Hazard Ratio (Fixed, 95% CI)	0.69 [0.42, 1.13]
8 Overall survival: dichotomous outcome	12	16028	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.81, 1.04]
8.1 Bisphosphonate vs control	10	14902	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.80, 1.03]
8.2 Immediate vs delayed	2	1126	Risk Ratio (M-H, Random, 95% CI)	2.14 [0.69, 6.60]
9 Overall survival by bisphosphonate: time-to-event outcome	10	15013	Hazard Ratio (Fixed, 95% CI)	0.90 [0.82, 0.98]
9.1 Zoledronate 4 mg iv every 4 weeks	5	7038	Hazard Ratio (Fixed, 95% CI)	0.91 [0.81, 1.03]
9.2 Clodronate 1600 mg oral daily	4	4981	Hazard Ratio (Fixed, 95% CI)	0.86 [0.74, 0.99]
9.3 Ibandronate 50 mg oral daily	1	2994	Hazard Ratio (Fixed, 95% CI)	1.04 [0.76, 1.42]
10 Overall survival by bisphosphonate: dichotomous outcome	12	16028	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.81, 1.04]
10.1 Zoledronate 4 mg iv every 4 weeks	6	7100	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.80, 1.11]
10.2 Clodronate 1600 mg oral daily	4	4981	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.60, 1.06]
10.3 Pamidronate 150 mg oral twice a day	1	953	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.94, 1.20]
10.4 Ibandronate 50 mg oral daily	1	2994	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.82, 1.49]
11 Overall survival by menopausal status: time-to-event outcome	9	14906	Hazard Ratio (Fixed, 95% CI)	0.90 [0.82, 0.99]
11.1 Pre- or perimenopausal	2	3501	Hazard Ratio (Fixed, 95% CI)	1.03 [0.86, 1.22]

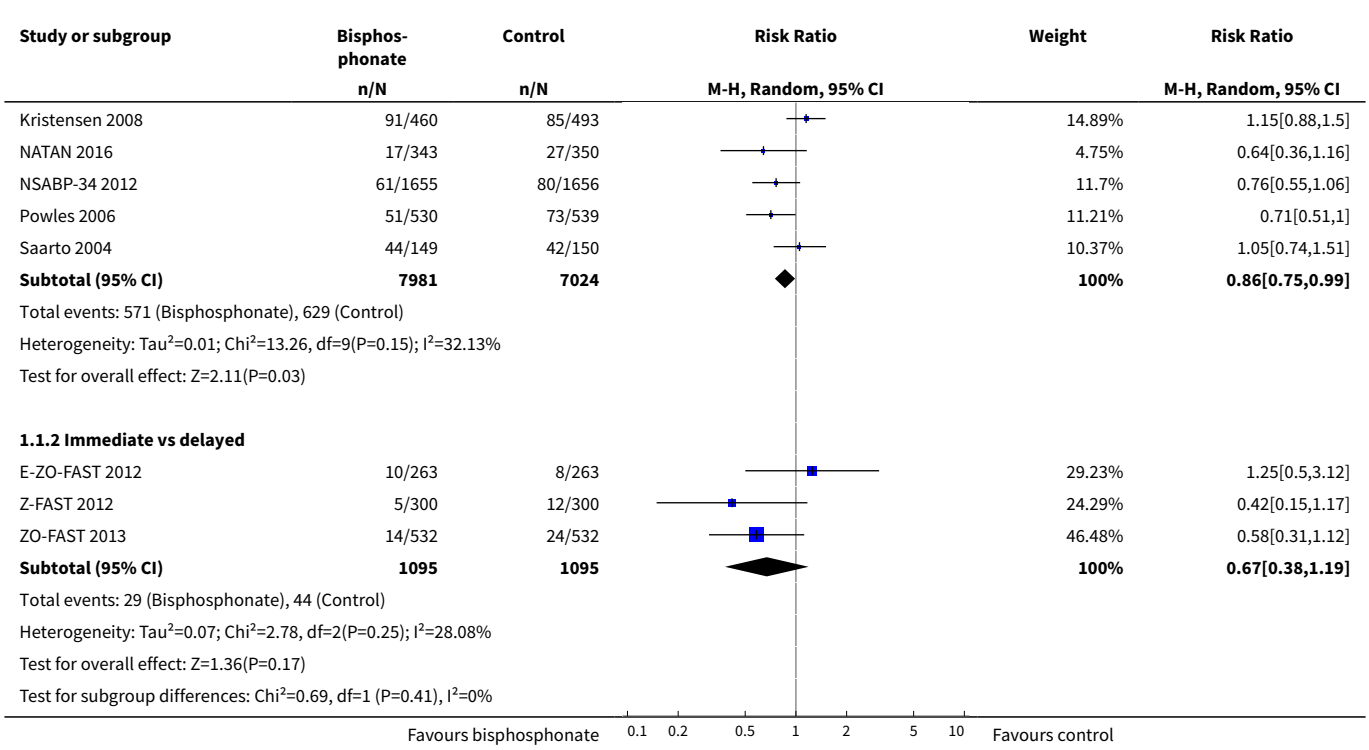
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.2 Postmenopausal	4	6048	Hazard Ratio (Fixed, 95% CI)	0.77 [0.66, 0.90]
11.3 Pre- or postmenopausal, or both, or status not available	5	5357	Hazard Ratio (Fixed, 95% CI)	0.95 [0.81, 1.10]
12 Overall survival by menopausal status: dichotomous outcome	12	16011	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.84, 1.03]
12.1 Pre- or perimenopausal	6	6191	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.96, 1.18]
12.2 Postmenopausal	9	8150	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.78, 1.03]
12.3 Pre- or postmenopausal or status not available	3	1670	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.50, 1.20]
13 Disease-free survival: time-to-event outcome	9	14242	Hazard Ratio (Fixed, 95% CI)	0.93 [0.86, 1.00]
13.1 Bisphosphonate vs control	7	12578	Hazard Ratio (Fixed, 95% CI)	0.94 [0.87, 1.02]
13.2 Immediate vs delayed bisphosphonate	2	1664	Hazard Ratio (Fixed, 95% CI)	0.72 [0.52, 1.01]
14 Disease-free survival: dichotomous outcome	10	15195	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.87, 1.04]
14.1 Bisphosphonate vs control	8	13531	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.89, 1.06]
14.2 Immediate vs delayed	2	1664	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.55, 1.02]
15 Disease-free survival by bisphosphonate: time-to-event outcome	9	14242	Hazard Ratio (Fixed, 95% CI)	0.93 [0.86, 1.00]
15.1 Zoledronate 4 mg iv every 4 weeks	6	7638	Hazard Ratio (Fixed, 95% CI)	0.89 [0.80, 0.98]
15.2 Clodronate 1600 mg oral daily	2	3610	Hazard Ratio (Fixed, 95% CI)	1.00 [0.87, 1.15]
15.3 Ibandronate 50 mg oral daily	1	2994	Hazard Ratio (Fixed, 95% CI)	0.95 [0.77, 1.17]
16 Disease-free survival by bisphosphonate: dichotomous outcome	10	15202	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.87, 1.04]
16.1 Zoledronate 4 mg iv every 4 weeks	6	7638	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.79, 0.98]
16.2 Clodronate 1600 mg oral daily	2	3617	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.79, 1.32]
16.3 Pamidronate 150 mg oral twice a day	1	953	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.98, 1.29]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.4 Ibandronate 50 mg oral daily	1	2994	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.83, 1.21]
17 Disease-free survival by menopausal status: time-to-event outcome	8	14106	Hazard Ratio (Fixed, 95% CI)	0.93 [0.86, 1.00]
17.1 Pre- or perimenopausal	4	5493	Hazard Ratio (Fixed, 95% CI)	1.01 [0.90, 1.13]
17.2 Postmenopausal	7	8314	Hazard Ratio (Fixed, 95% CI)	0.82 [0.74, 0.91]
17.3 Pre- or postmenopausal or status not available	1	299	Hazard Ratio (Fixed, 95% CI)	1.53 [1.11, 2.11]
18 Disease-free survival by menopausal status: dichotomous outcome	10	15150	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.88, 1.03]
18.1 Pre- or perimenopausal	5	4997	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.96, 1.15]
18.2 Postmenopausal	8	6536	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.77, 0.97]
18.3 Pre- or postmenopausal or both, or status not available	2	3617	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.79, 1.32]
19 Fracture incidence	10	13212	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.57, 0.90]
19.1 Bisphosphonate vs control	6	7602	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.54, 1.08]
19.2 Denosumab vs placebo	1	3420	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.41, 0.67]
19.3 Immediate vs delayed bisphosphonate	3	2190	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.57, 1.13]

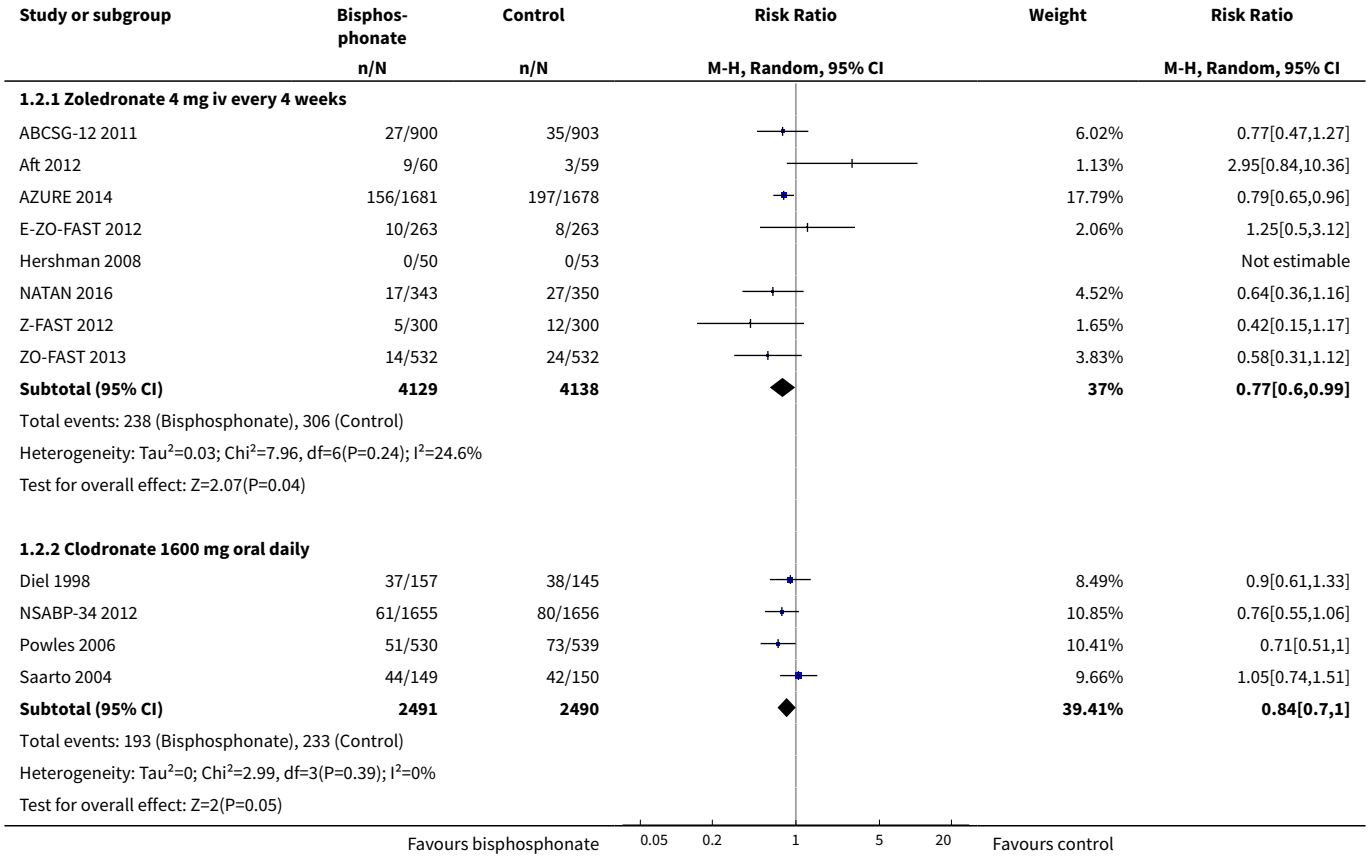
Analysis 1.1. Comparison 1 Early Breast Cancer (EBC), Outcome 1 Bone metastases.

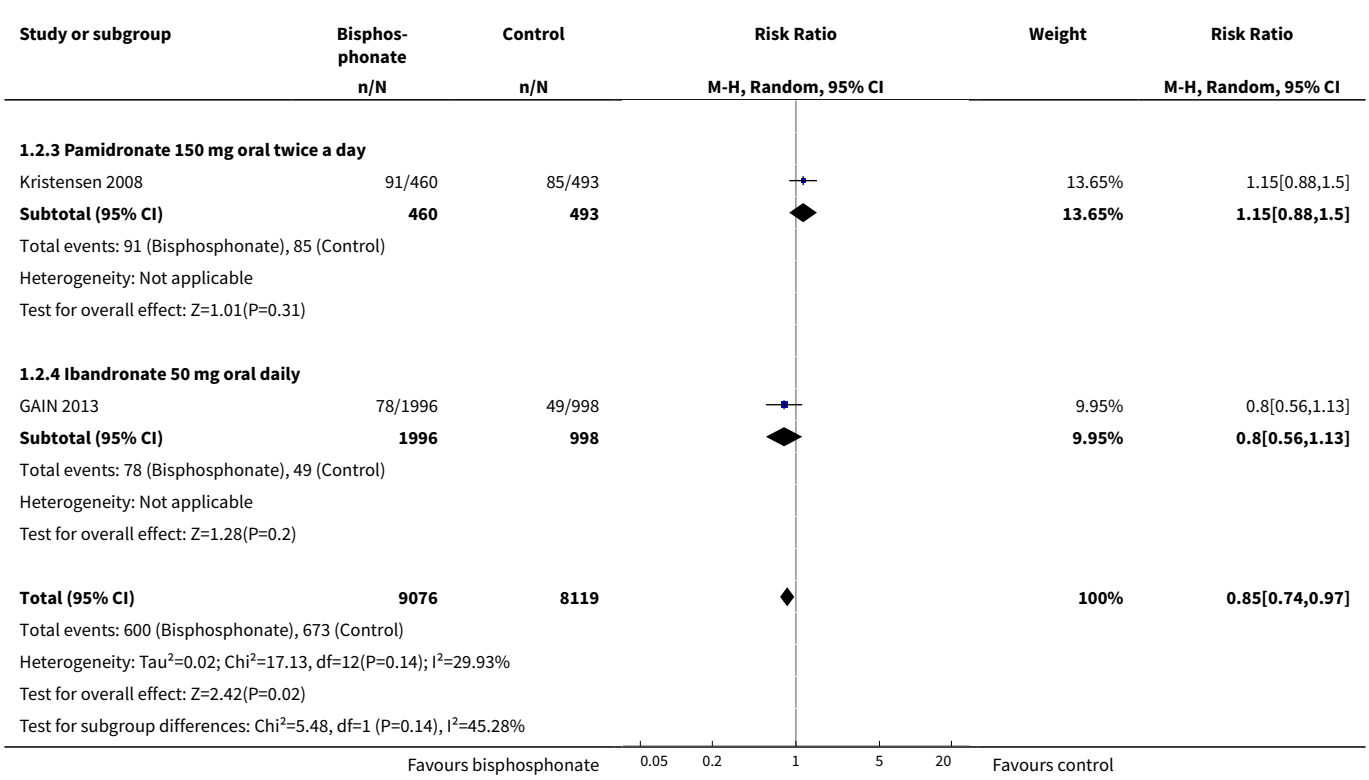
Study or subgroup	Bisphosphonate n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Bisphosphonate vs control					
ABCSG-12 2011	27/900	35/903		6.37%	0.77[0.47,1.27]
Aft 2012	9/60	3/59		1.17%	2.95[0.84,10.36]
AZURE 2014	156/1681	197/1678		19.76%	0.79[0.65,0.96]
Diel 1998	37/157	38/145		9.07%	0.9[0.61,1.33]
GAIN 2013	78/1996	49/998		10.69%	0.8[0.56,1.13]
Hershman 2008	0/50	0/53			Not estimable



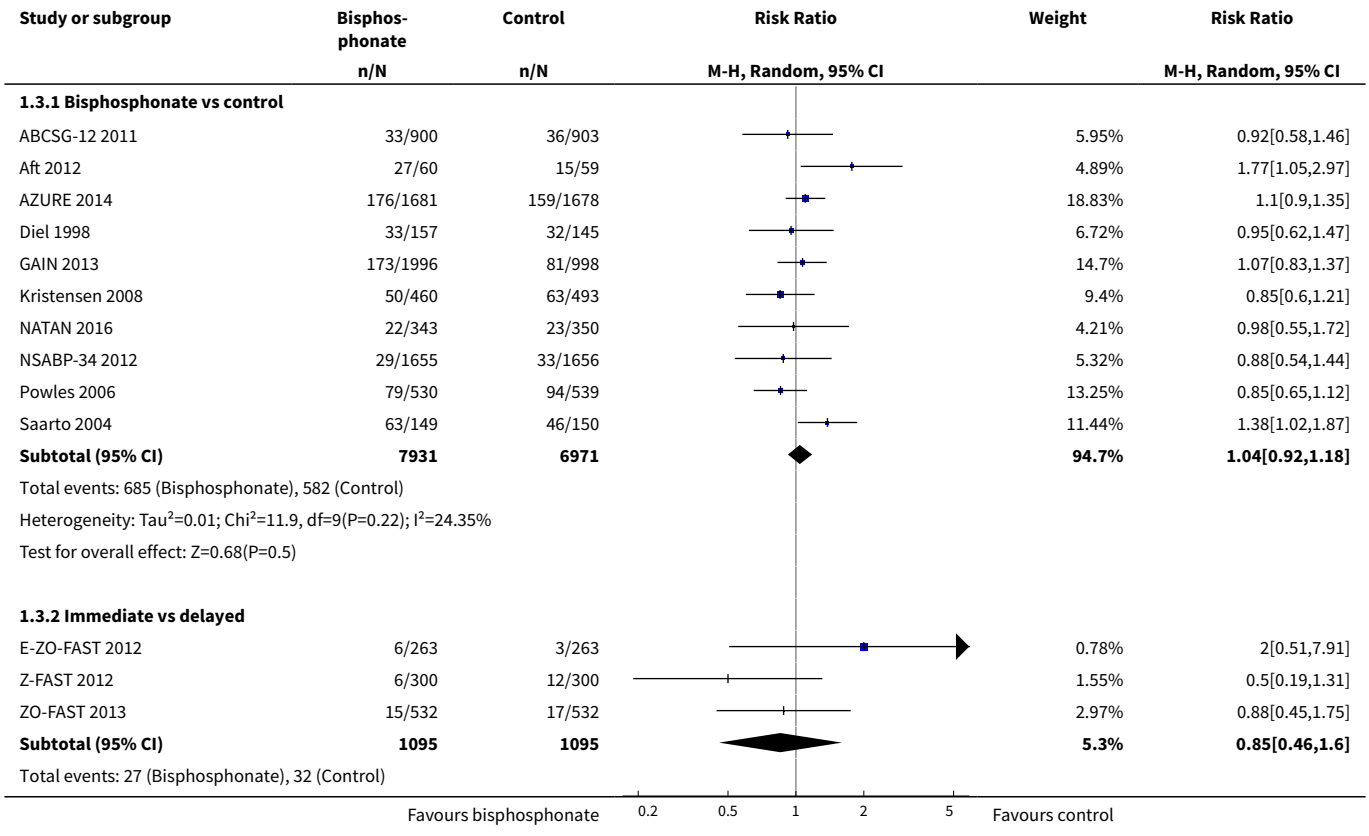


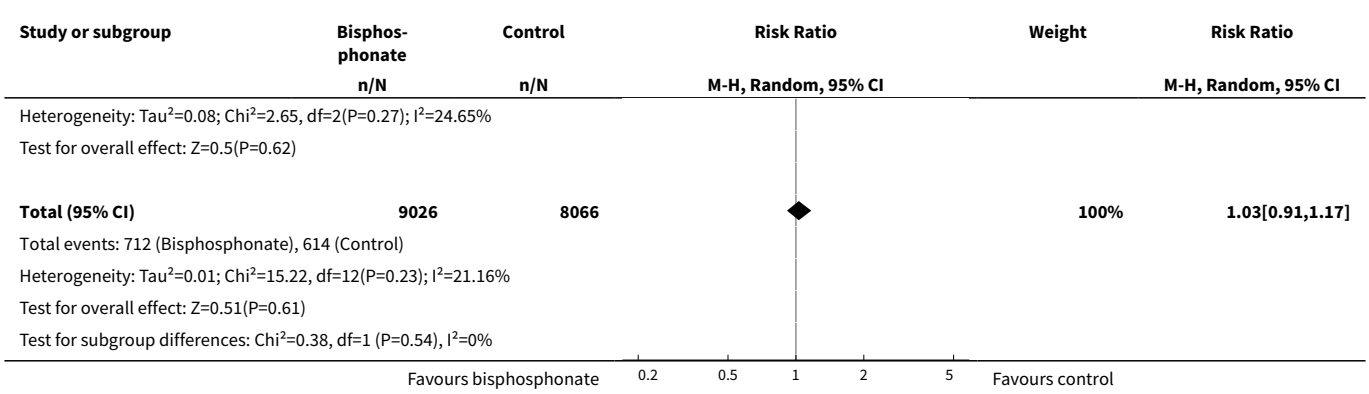
Analysis 1.2. Comparison 1 Early Breast Cancer (EBC), Outcome 2 Bone metastases by bisphosphonate.



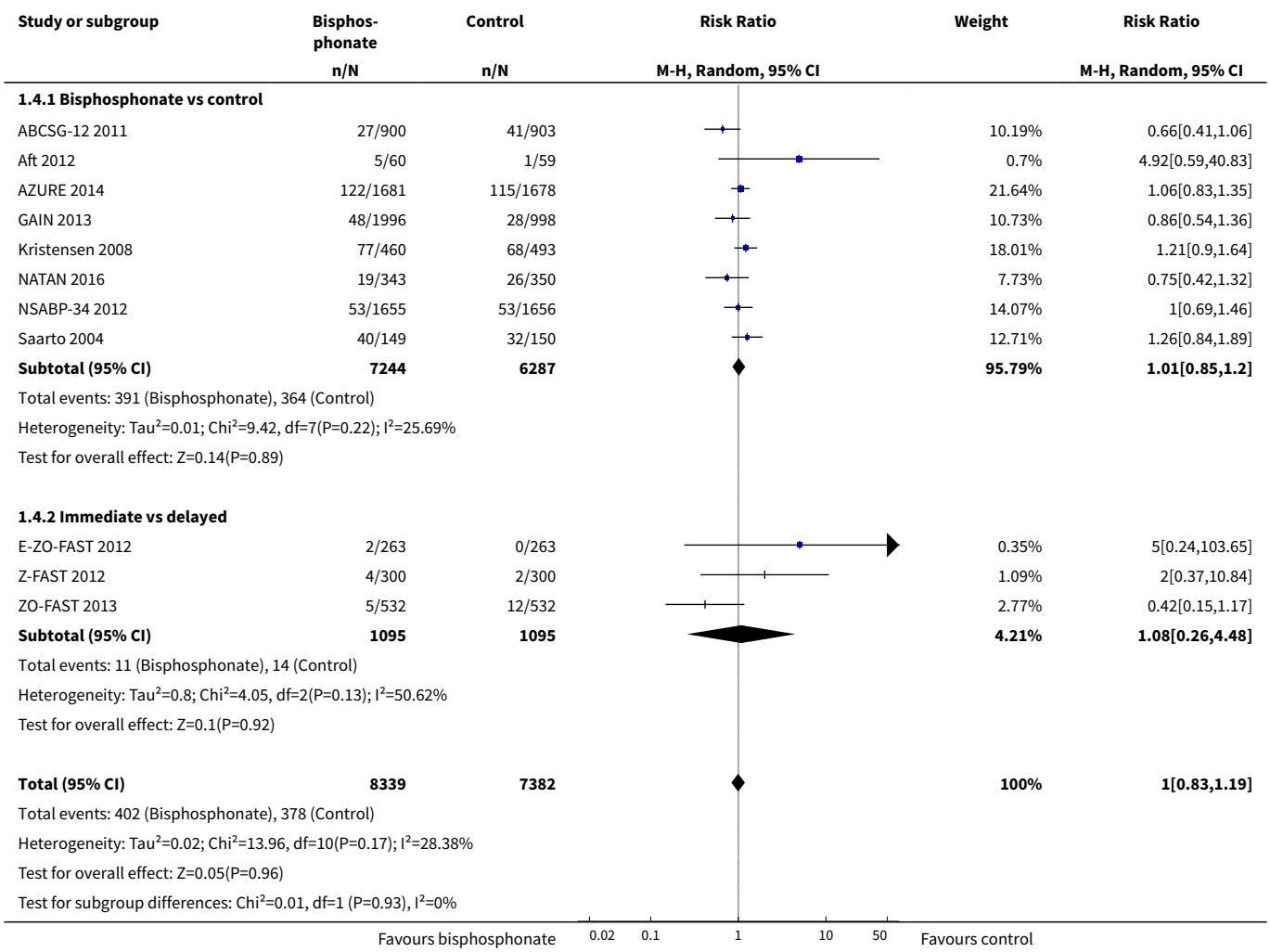


Analysis 1.3. Comparison 1 Early Breast Cancer (EBC), Outcome 3 Visceral recurrence.



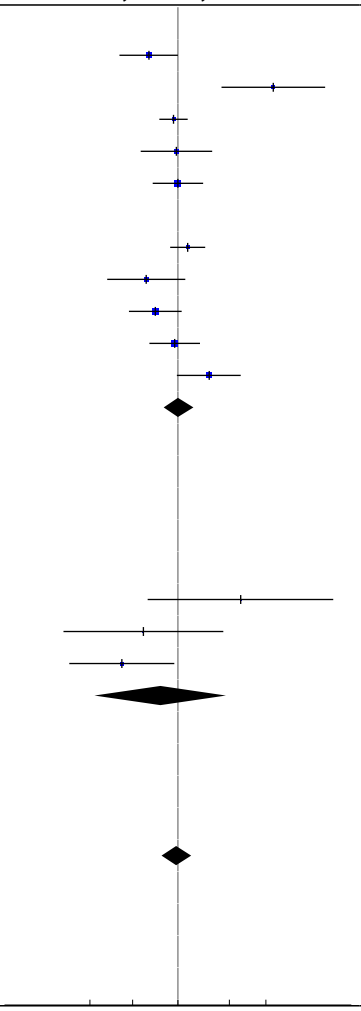


Analysis 1.4. Comparison 1 Early Breast Cancer (EBC), Outcome 4 Locoregional recurrence.



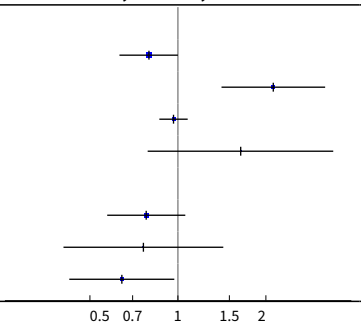
Analysis 1.5. Comparison 1 Early Breast Cancer (EBC), Outcome 5 Overall recurrence.

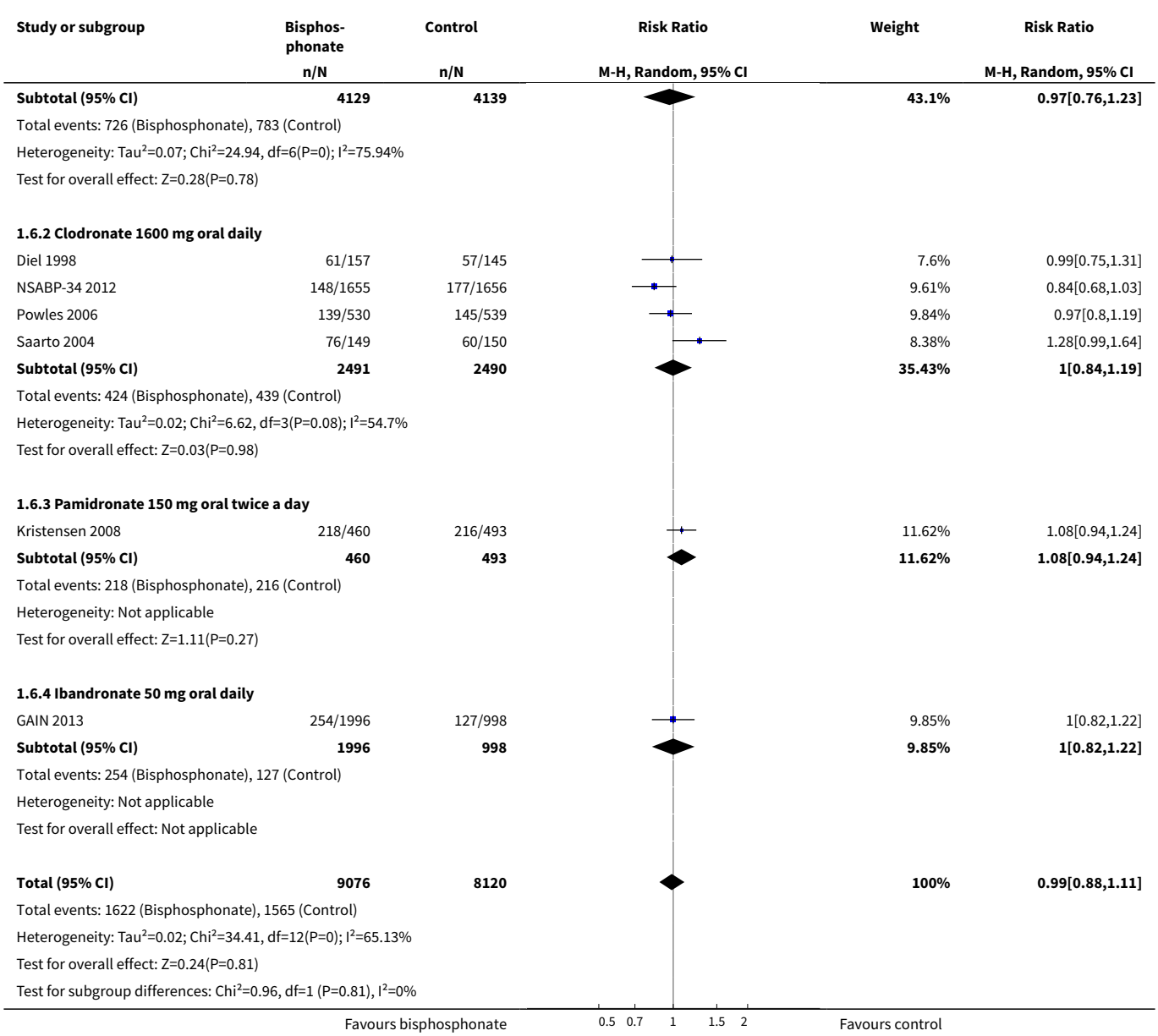
Study or subgroup	Bisphosphonate n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Bisphosphonate vs control					
ABCSG-12 2011	111/900	140/903		8.93%	0.8[0.63,1]
Aft 2012	41/60	19/59		5.05%	2.12[1.41,3.19]
AZURE 2014	448/1681	463/1678		12.38%	0.97[0.86,1.08]
Diel 1998	61/157	57/145		7.6%	0.99[0.75,1.31]
GAIN 2013	254/1996	127/998		9.85%	1[0.82,1.22]
Hershman 2008	0/50	0/53			Not estimable
Kristensen 2008	218/460	216/493		11.62%	1.08[0.94,1.24]
NATAN 2016	58/343	76/350		6.98%	0.78[0.57,1.06]
NSABP-34 2012	148/1655	177/1656		9.61%	0.84[0.68,1.03]
Powles 2006	139/530	145/539		9.84%	0.97[0.8,1.19]
Saarto 2004	76/149	60/150		8.38%	1.28[0.99,1.64]
Subtotal (95% CI)	**7981**	**7024**		**90.24%**	**1[0.89,1.13]**
Total events: 1554 (Bisphosphonate), 1480 (Control)					
Heterogeneity: Tau^2=0.02; Chi^2=27.71, df=9(P=0); I^2=67.52%					
Test for overall effect: Z=0.07(P=0.95)					
1.5.2 Immediate vs delayed					
E-ZO-FAST 2012	18/263	11/263		2.1%	1.64[0.79,3.4]
Z-FAST 2012	16/300	21/300		2.68%	0.76[0.41,1.43]
ZO-FAST 2013	34/532	53/533		4.97%	0.64[0.43,0.97]
Subtotal (95% CI)	**1095**	**1096**		**9.76%**	**0.87[0.52,1.46]**
Total events: 68 (Bisphosphonate), 85 (Control)					
Heterogeneity: Tau^2=0.12; Chi^2=4.79, df=2(P=0.09); I^2=58.23%					
Test for overall effect: Z=0.52(P=0.6)					
Total (95% CI)	**9076**	**8120**		**100%**	**0.99[0.88,1.11]**
Total events: 1622 (Bisphosphonate), 1565 (Control)					
Heterogeneity: Tau^2=0.02; Chi^2=34.41, df=12(P=0); I^2=65.13%					
Test for overall effect: Z=0.24(P=0.81)					
Test for subgroup differences: Chi^2=0.27, df=1 (P=0.6), I^2=0%					



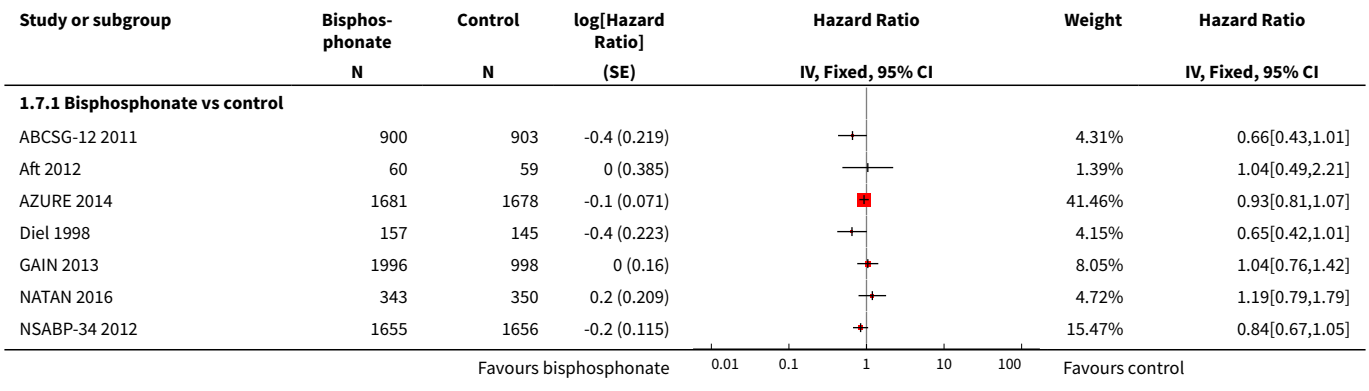
Analysis 1.6. Comparison 1 Early Breast Cancer (EBC), Outcome 6 Overall recurrence by bisphosphonate.

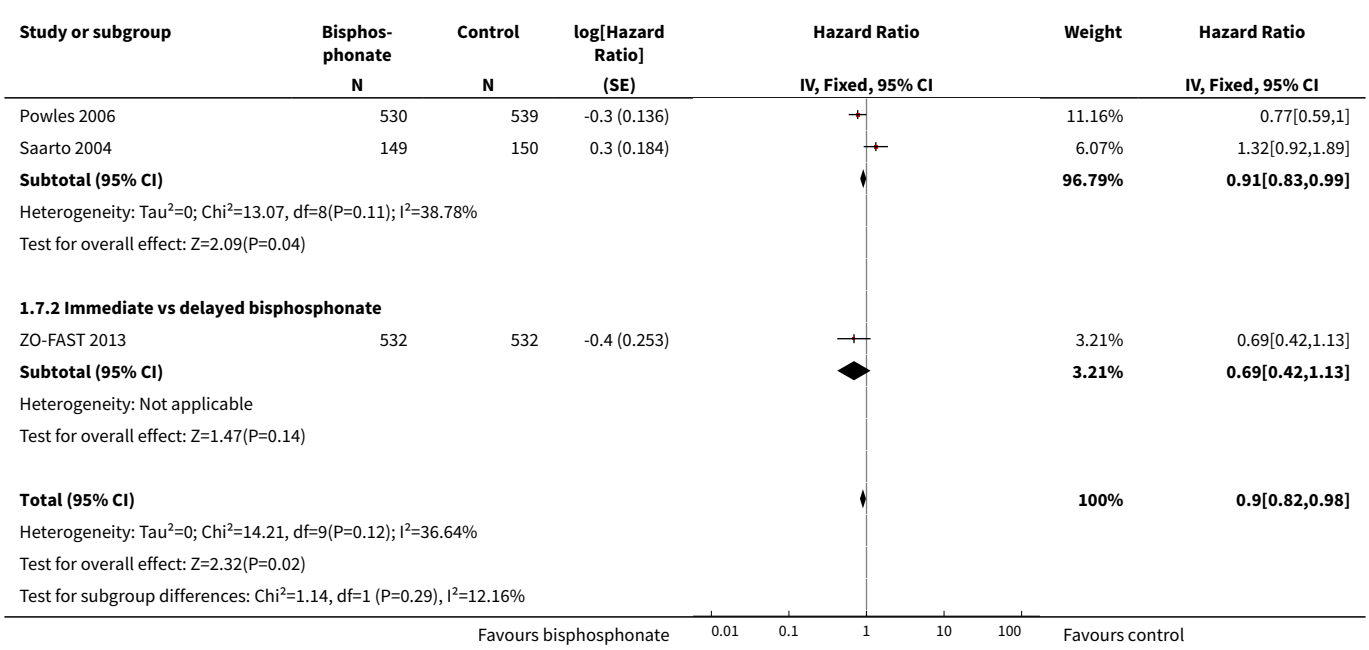
Study or subgroup	Bisphosphonate n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 Zoledronate 4 mg iv every 4 weeks					
ABCSG-12 2011	111/900	140/903		8.93%	0.8[0.63,1]
Aft 2012	41/60	19/59		5.05%	2.12[1.41,3.19]
AZURE 2014	448/1681	463/1678		12.38%	0.97[0.86,1.08]
E-ZO-FAST 2012	18/263	11/263		2.1%	1.64[0.79,3.4]
Hershman 2008	0/50	0/53			Not estimable
NATAN 2016	58/343	76/350		6.98%	0.78[0.57,1.06]
Z-FAST 2012	16/300	21/300		2.68%	0.76[0.41,1.43]
ZO-FAST 2013	34/532	53/533		4.97%	0.64[0.43,0.97]



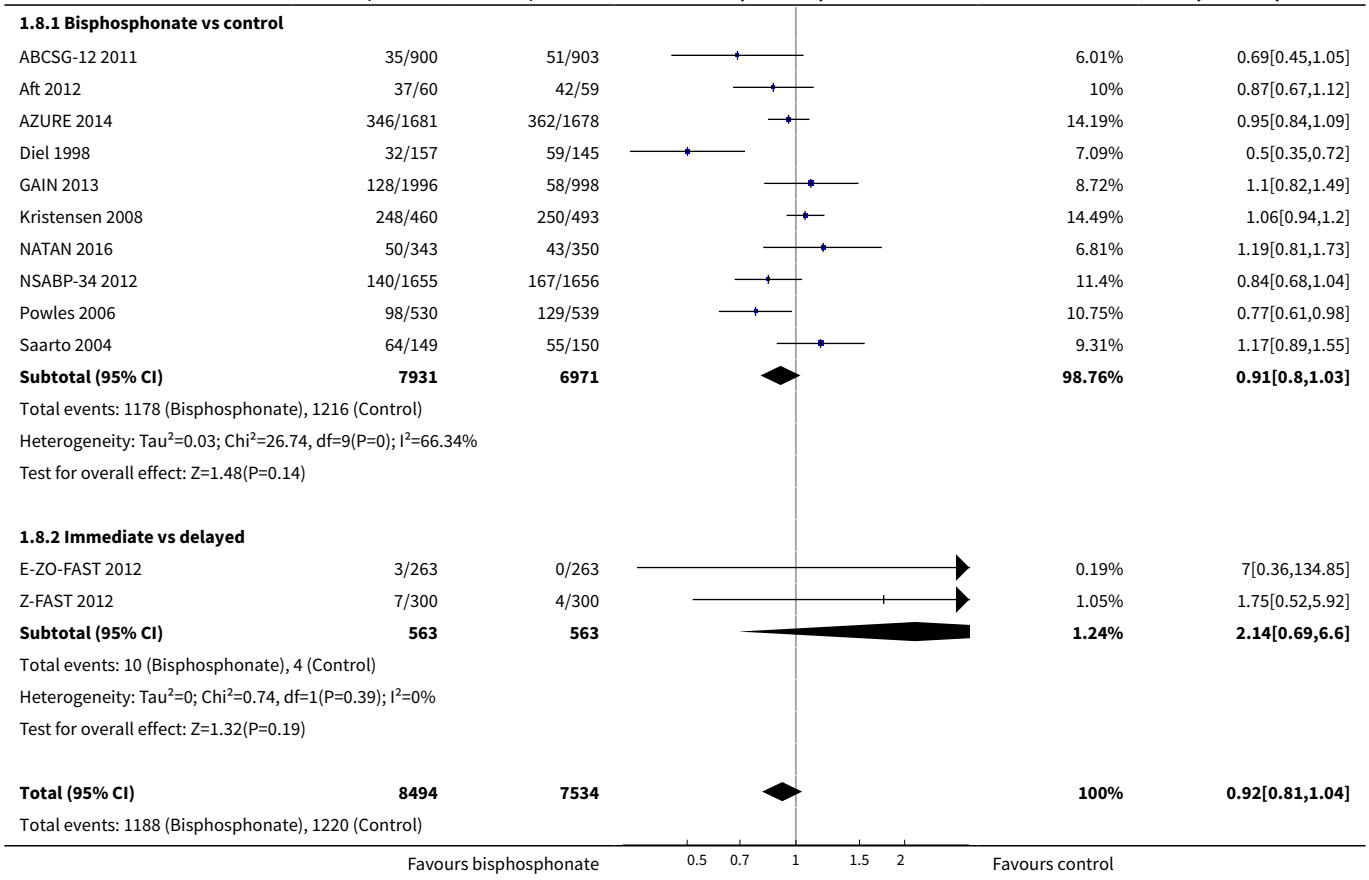


Analysis 1.7. Comparison 1 Early Breast Cancer (EBC), Outcome 7 Overall survival: time-to-event outcome.

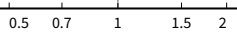




Analysis 1.8. Comparison 1 Early Breast Cancer (EBC), Outcome 8 Overall survival: dichotomous outcome.



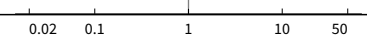
Study or subgroup	Bisphos-phonate	Control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Heterogeneity: Tau²=0.03; Chi²=29.4, df=11(P=0); I²=62.58%					
Test for overall effect: Z=1.32(P=0.19)					
Test for subgroup differences: Chi²=2.2, df=1 (P=0.14), I²=54.54%					



Favours bisphosphonate — Favours control

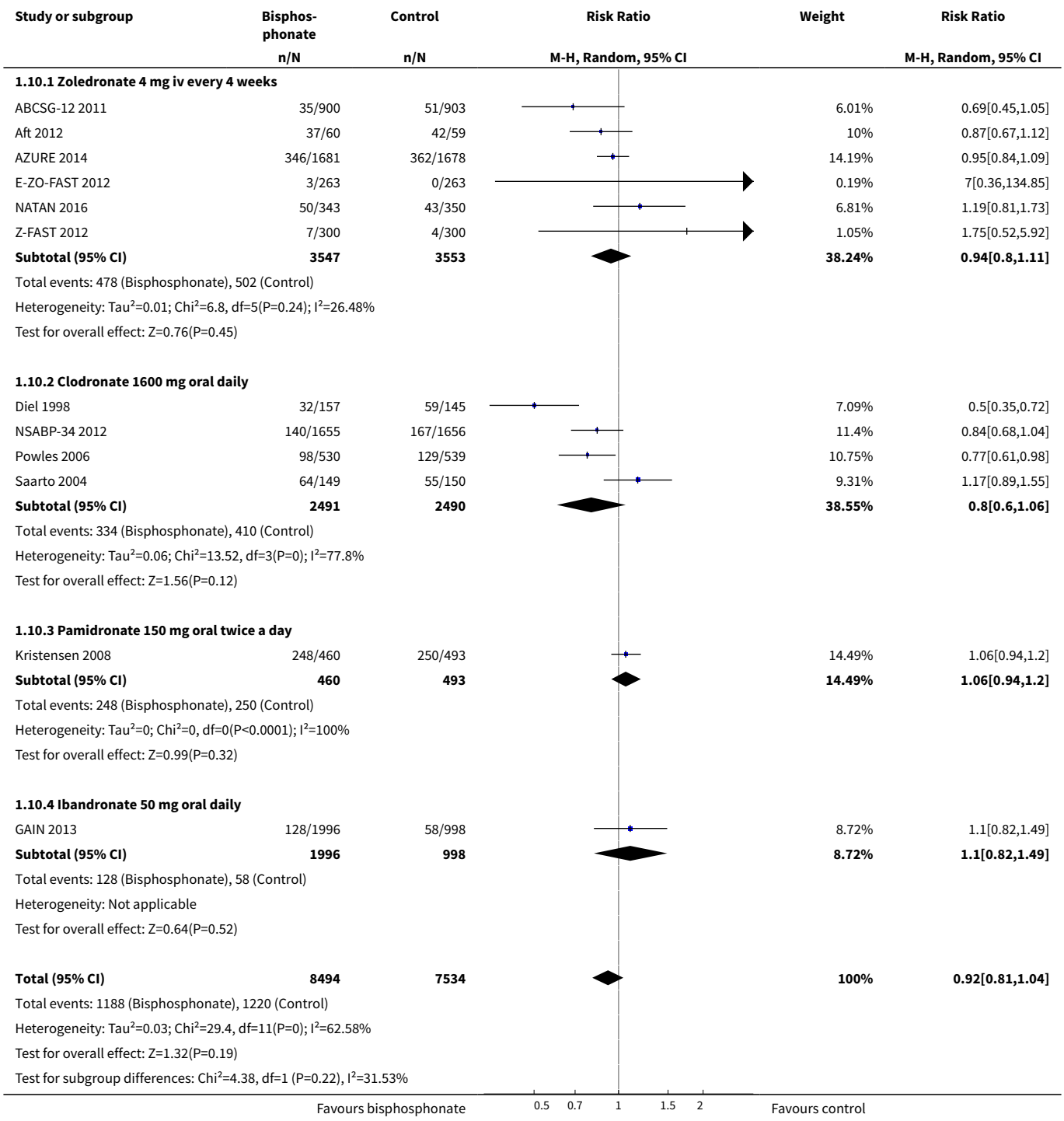
Analysis 1.9. Comparison 1 Early Breast Cancer (EBC), Outcome 9 Overall survival by bisphosphonate: time-to-event outcome.

Study or subgroup	Bisphos-phonate	Control	log[Hazard Ratio]	Hazard Ratio	Weight	Hazard Ratio
	N	N	(SE)	IV, Fixed, 95% CI		IV, Fixed, 95% CI
1.9.1 Zoledronate 4 mg iv every 4 weeks						
ABCSG-12 2011	900	903	-0.4 (0.219)		4.31%	0.66[0.43,1.01]
Aft 2012	60	59	0 (0.385)		1.39%	1.04[0.49,2.21]
AZURE 2014	1681	1678	-0.1 (0.071)		41.46%	0.93[0.81,1.07]
NATAN 2016	343	350	0.2 (0.209)		4.72%	1.19[0.79,1.79]
ZO-FAST 2013	532	532	-0.4 (0.253)		3.21%	0.69[0.42,1.13]
Subtotal (95% CI)					**55.09%**	**0.91[0.81,1.03]**
Heterogeneity: Tau²=0; Chi²=5.22, df=4(P=0.27); I²=23.31%						
Test for overall effect: Z=1.52(P=0.13)						
1.9.2 Clodronate 1600 mg oral daily						
Diel 1998	157	145	-0.4 (0.223)		4.15%	0.65[0.42,1.01]
NSABP-34 2012	1655	1656	-0.2 (0.115)		15.47%	0.84[0.67,1.05]
Powles 2006	530	539	-0.3 (0.136)		11.16%	0.77[0.59,1]
Saarto 2004	149	150	0.3 (0.184)		6.07%	1.32[0.92,1.89]
Subtotal (95% CI)					**36.86%**	**0.86[0.74,0.99]**
Heterogeneity: Tau²=0; Chi²=7.69, df=3(P=0.05); I²=60.98%						
Test for overall effect: Z=2.07(P=0.04)						
1.9.3 Ibandronate 50 mg oral daily						
GAIN 2013	1996	998	0 (0.16)		8.05%	1.04[0.76,1.42]
Subtotal (95% CI)					**8.05%**	**1.04[0.76,1.42]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.25(P=0.81)						
Total (95% CI)					**100%**	**0.9[0.82,0.98]**
Heterogeneity: Tau²=0; Chi²=14.21, df=9(P=0.12); I²=36.64%						
Test for overall effect: Z=2.32(P=0.02)						
Test for subgroup differences: Chi²=1.3, df=1 (P=0.52), I²=0%						



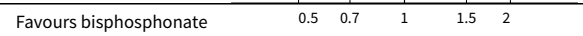
Favours bisphosphonate — Favours control

Analysis 1.10. Comparison 1 Early Breast Cancer (EBC), Outcome 10 Overall survival by bisphosphonate: dichotomous outcome.



Analysis 1.11. Comparison 1 Early Breast Cancer (EBC), Outcome 11 Overall survival by menopausal status: time-to-event outcome.

Study or subgroup	Bisphosphonate N	Control N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Fixed, 95% CI	Weight	Hazard Ratio IV, Fixed, 95% CI
1.11.1 Pre- or perimenopausal						
NSABP-34 2012	594	589	-0.1 (0.226)		4.44%	0.95[0.61,1.48]
AZURE 2014	1162	1156	0 (0.097)		24.09%	1.04[0.86,1.26]
Subtotal (95% CI)					**28.53%**	**1.03[0.86,1.22]**
Heterogeneity: Tau^2=0; Chi^2=0.14, df=1(P=0.71); I^2=0%						
Test for overall effect: Z=0.28(P=0.78)						
1.11.2 Postmenopausal						
ABCSG-12 2011	900	903	-0.4 (0.219)		4.74%	0.66[0.43,1.01]
ZO-FAST 2013	532	532	-0.4 (0.253)		3.53%	0.69[0.42,1.13]
NSABP-34 2012	1068	1072	-0.2 (0.138)		11.85%	0.8[0.61,1.05]
AZURE 2014	519	522	-0.2 (0.128)		13.79%	0.81[0.63,1.04]
Subtotal (95% CI)					**33.92%**	**0.77[0.66,0.9]**
Heterogeneity: Tau^2=0; Chi^2=0.92, df=3(P=0.82); I^2=0%						
Test for overall effect: Z=3.19(P=0)						
1.11.3 Pre- or postmenopausal, or both, or status not available						
Diel 1998	157	145	-0.4 (0.223)		4.57%	0.65[0.42,1.01]
Powles 2006	530	539	-0.3 (0.136)		12.27%	0.77[0.59,1]
GAIN 2013	1996	998	0 (0.16)		8.85%	1.04[0.76,1.42]
NATAN 2016	343	350	0.2 (0.209)		5.19%	1.19[0.79,1.79]
Saarto 2004	149	150	0.3 (0.184)		6.68%	1.32[0.92,1.89]
Subtotal (95% CI)					**37.56%**	**0.95[0.81,1.1]**
Heterogeneity: Tau^2=0; Chi^2=9.96, df=4(P=0.04); I^2=59.84%						
Test for overall effect: Z=0.71(P=0.48)						
Total (95% CI)					**100%**	**0.9[0.82,0.99]**
Heterogeneity: Tau^2=0; Chi^2=17.16, df=10(P=0.07); I^2=41.74%						
Test for overall effect: Z=2.14(P=0.03)						
Test for subgroup differences: Chi^2=6.15, df=1 (P=0.05), I^2=67.49%						



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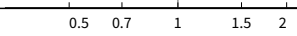
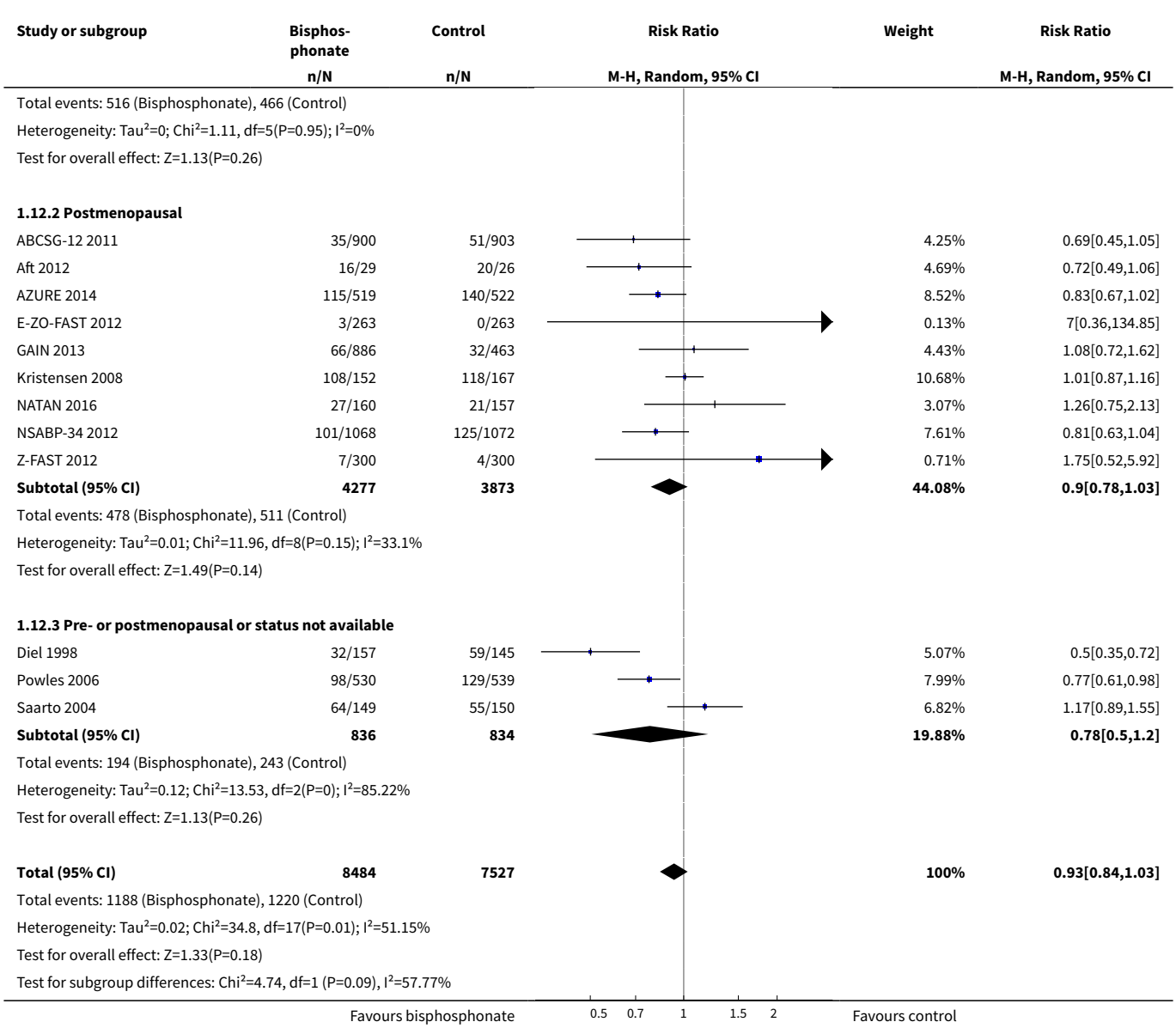
Analysis 1.12. Comparison 1 Early Breast Cancer (EBC), Outcome 12 Overall survival by menopausal status: dichotomous outcome.

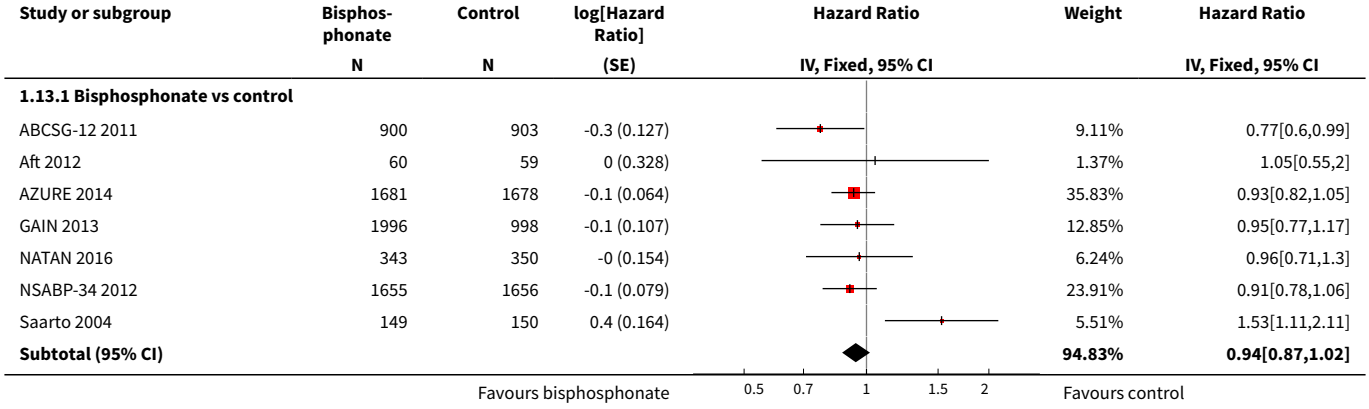
Study or subgroup	Bisphosphonate n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.12.1 Pre- or perimenopausal					
Aft 2012	21/31	22/33		5.5%	1.02[0.72,1.43]
AZURE 2014	231/1162	222/1156		9.96%	1.04[0.88,1.22]
GAIN 2013	62/1098	26/533		3.91%	1.16[0.74,1.81]
Kristensen 2008	140/308	132/326		9.53%	1.12[0.94,1.34]
NATAN 2016	23/178	22/183		2.89%	1.07[0.62,1.86]
NSABP-34 2012	39/594	42/589		4.24%	0.92[0.6,1.4]
Subtotal (95% CI)	**3371**	**2820**		**36.04%**	**1.06[0.96,1.18]**

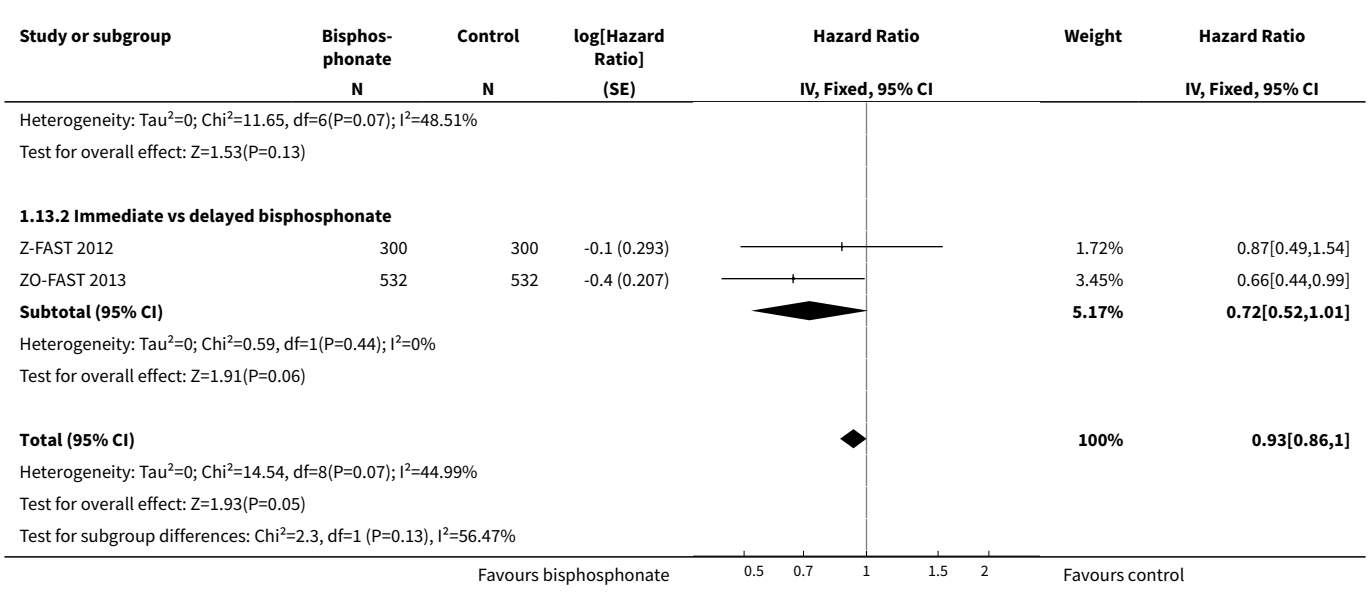


Favours bisphosphonate — Favours control

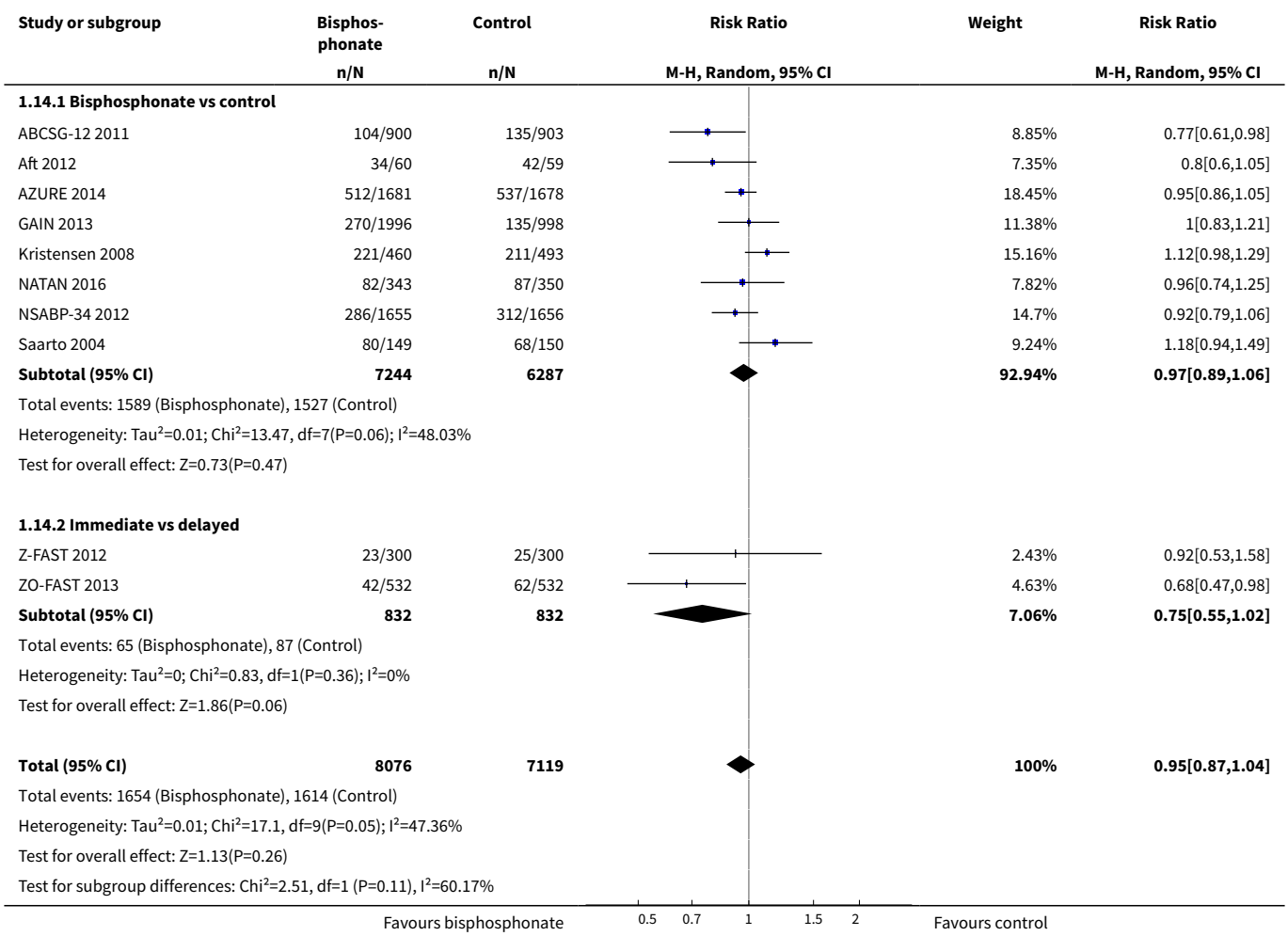


Analysis 1.13. Comparison 1 Early Breast Cancer (EBC), Outcome 13 Disease-free survival: time-to-event outcome.

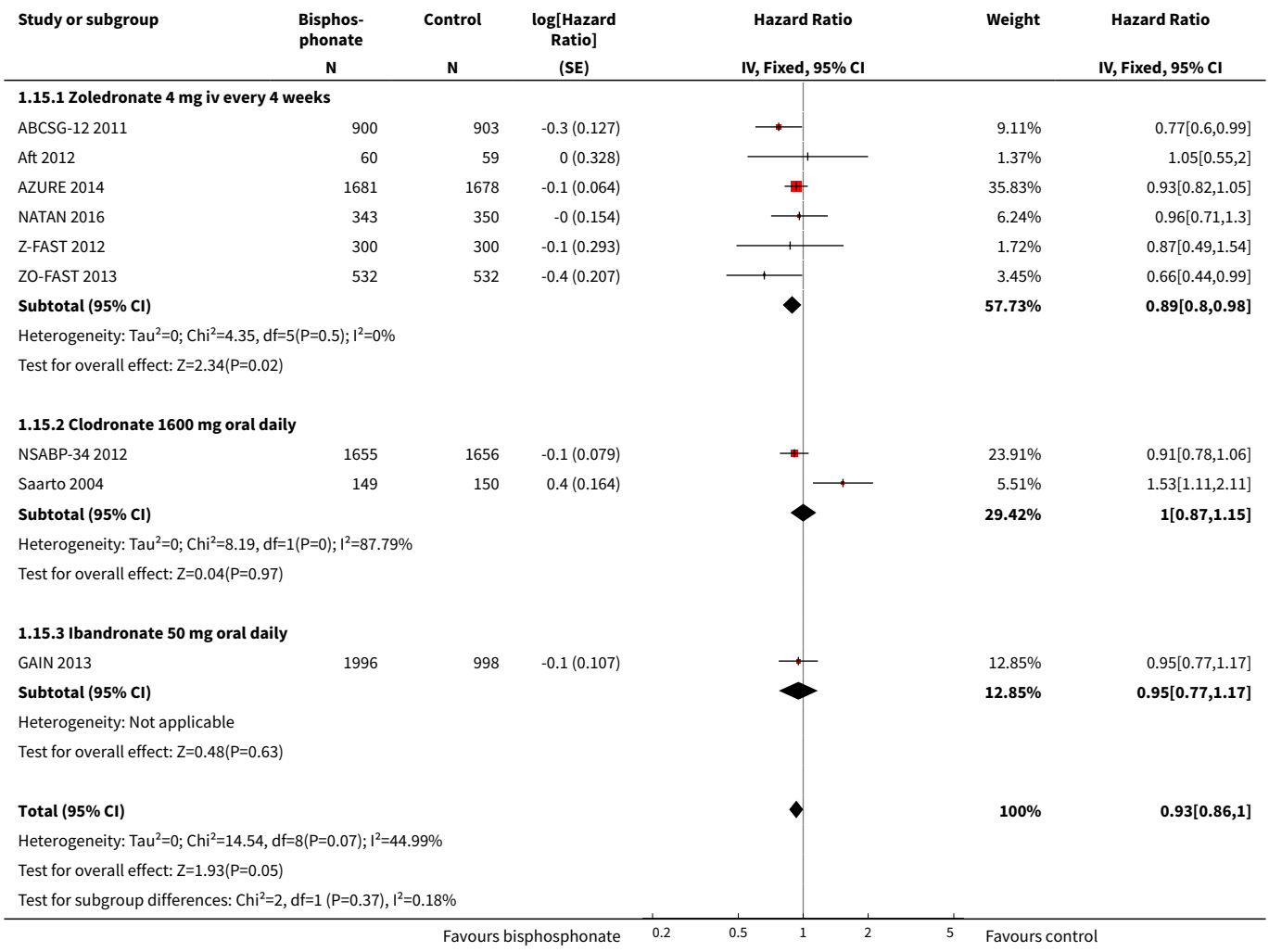




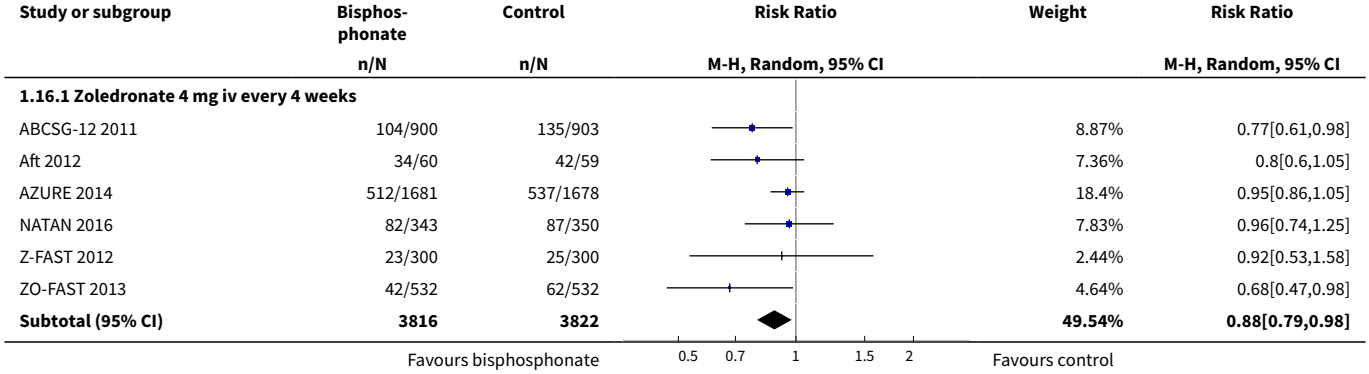
Analysis 1.14. Comparison 1 Early Breast Cancer (EBC), Outcome 14 Disease-free survival: dichotomous outcome.

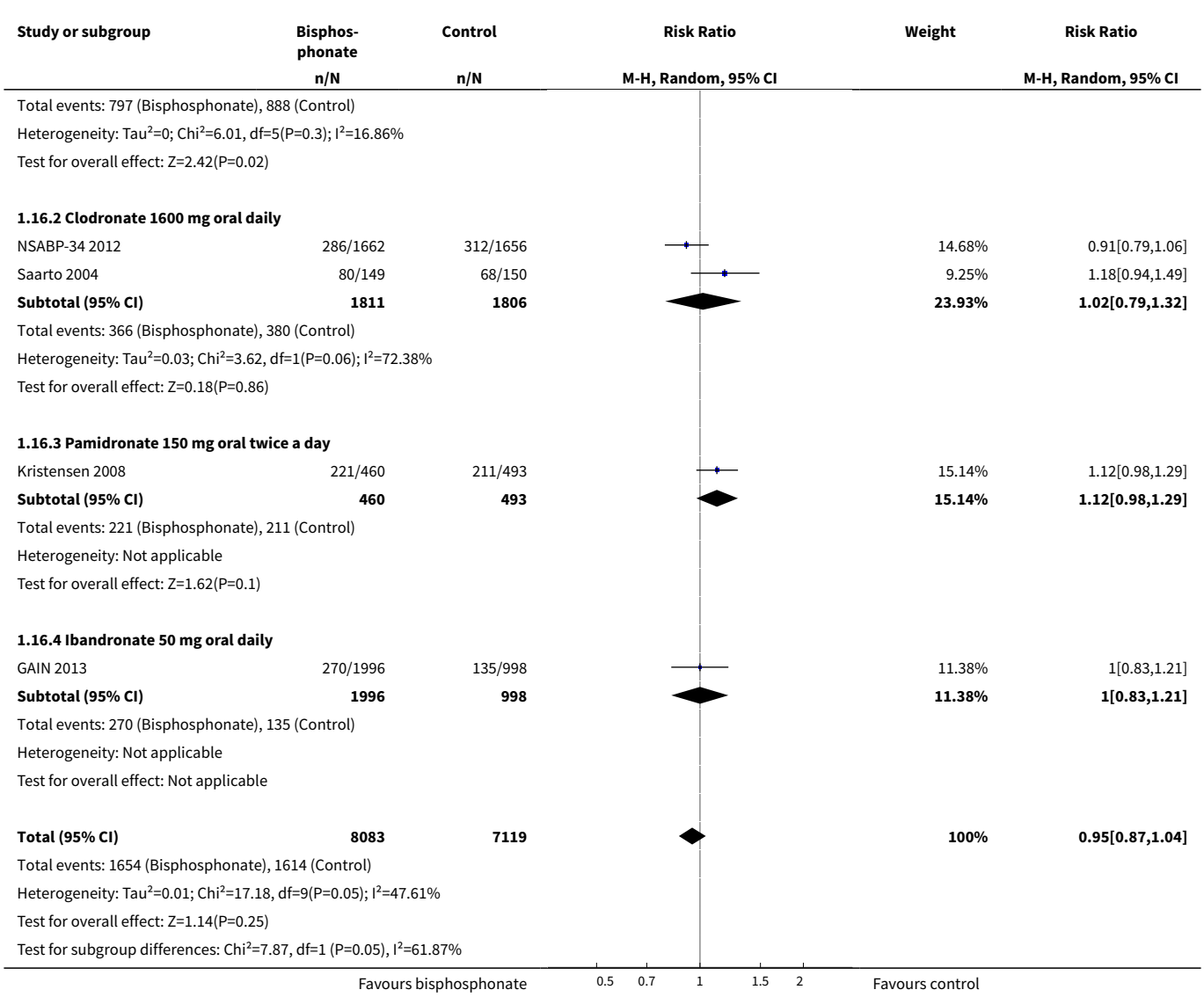


Analysis 1.15. Comparison 1 Early Breast Cancer (EBC), Outcome 15 Disease-free survival by bisphosphonate: time-to-event outcome.

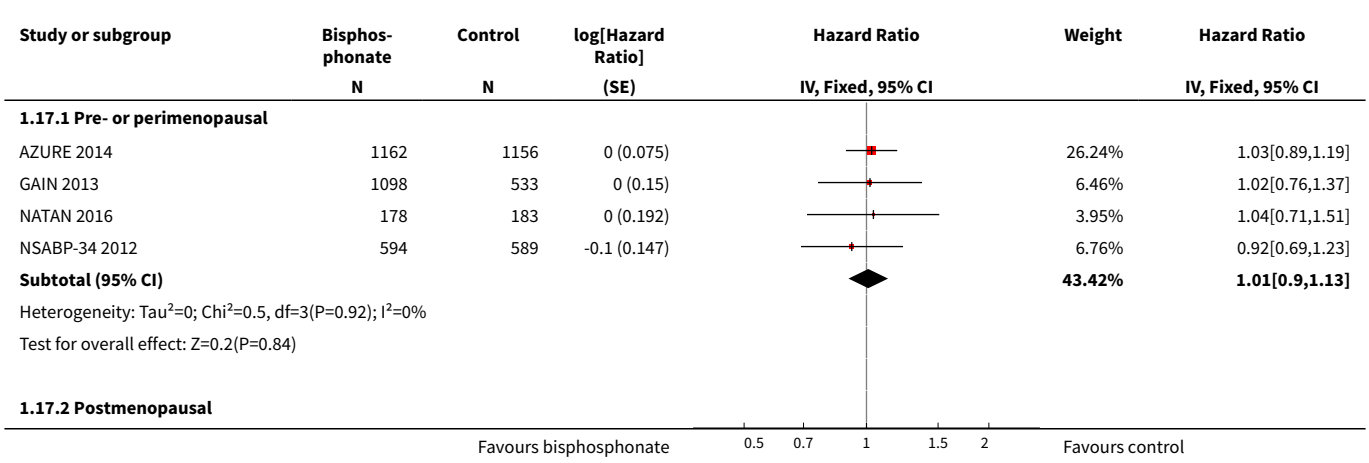


Analysis 1.16. Comparison 1 Early Breast Cancer (EBC), Outcome 16 Disease-free survival by bisphosphonate: dichotomous outcome.

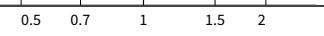




Analysis 1.17. Comparison 1 Early Breast Cancer (EBC), Outcome 17 Disease-free survival by menopausal status: time-to-event outcome.



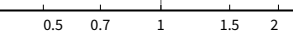
Study or subgroup	Bisphos-phonate N	Control N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Fixed, 95% CI	Weight	Hazard Ratio IV, Fixed, 95% CI
ABCSG-12 2011	900	903	-0.3 (0.127)		8.99%	0.77[0.6,0.99]
AZURE 2014	519	522	-0.3 (0.102)		13.89%	0.77[0.63,0.94]
GAIN 2013	886	463	-0.1 (0.151)		6.42%	0.9[0.67,1.21]
NATAN 2016	160	157	-0.2 (0.26)		2.16%	0.83[0.5,1.38]
NSABP-34 2012	1068	1072	-0.1 (0.1)		14.59%	0.9[0.74,1.09]
Z-FAST 2012	300	300	-0.1 (0.293)		1.7%	0.87[0.49,1.54]
ZO-FAST 2013	532	532	-0.4 (0.207)		3.4%	0.66[0.44,0.99]
Subtotal (95% CI)					**51.15%**	**0.82[0.74,0.91]**
Heterogeneity: Tau²=0; Chi²=3.02, df=6(P=0.81); I²=0%						
Test for overall effect: Z=3.75(P=0)						
1.17.3 Pre- or postmenopausal or status not available						
Saarto 2004	149	150	0.4 (0.164)		5.43%	1.53[1.11,2.11]
Subtotal (95% CI)					**5.43%**	**1.53[1.11,2.11]**
Heterogeneity: Not applicable						
Test for overall effect: Z=2.6(P=0.01)						
Total (95% CI)					**100%**	**0.93[0.86,1]**
Heterogeneity: Tau²=0; Chi²=20.59, df=11(P=0.04); I²=46.58%						
Test for overall effect: Z=1.95(P=0.05)						
Test for subgroup differences: Chi²=17.07, df=1 (P=0), I²=88.29%						



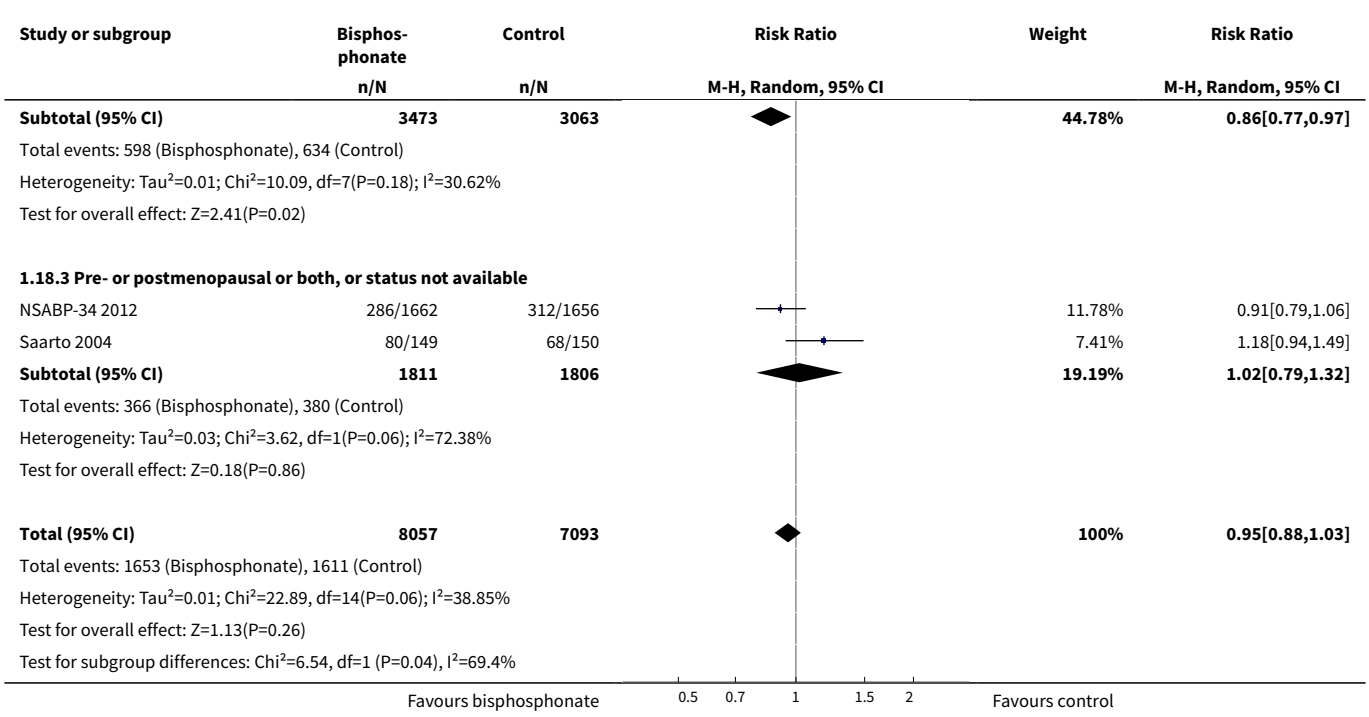
Favours bisphosphonate — Favours control

Analysis 1.18. Comparison 1 Early Breast Cancer (EBC), Outcome 18 Disease-free survival by menopausal status: dichotomous outcome.

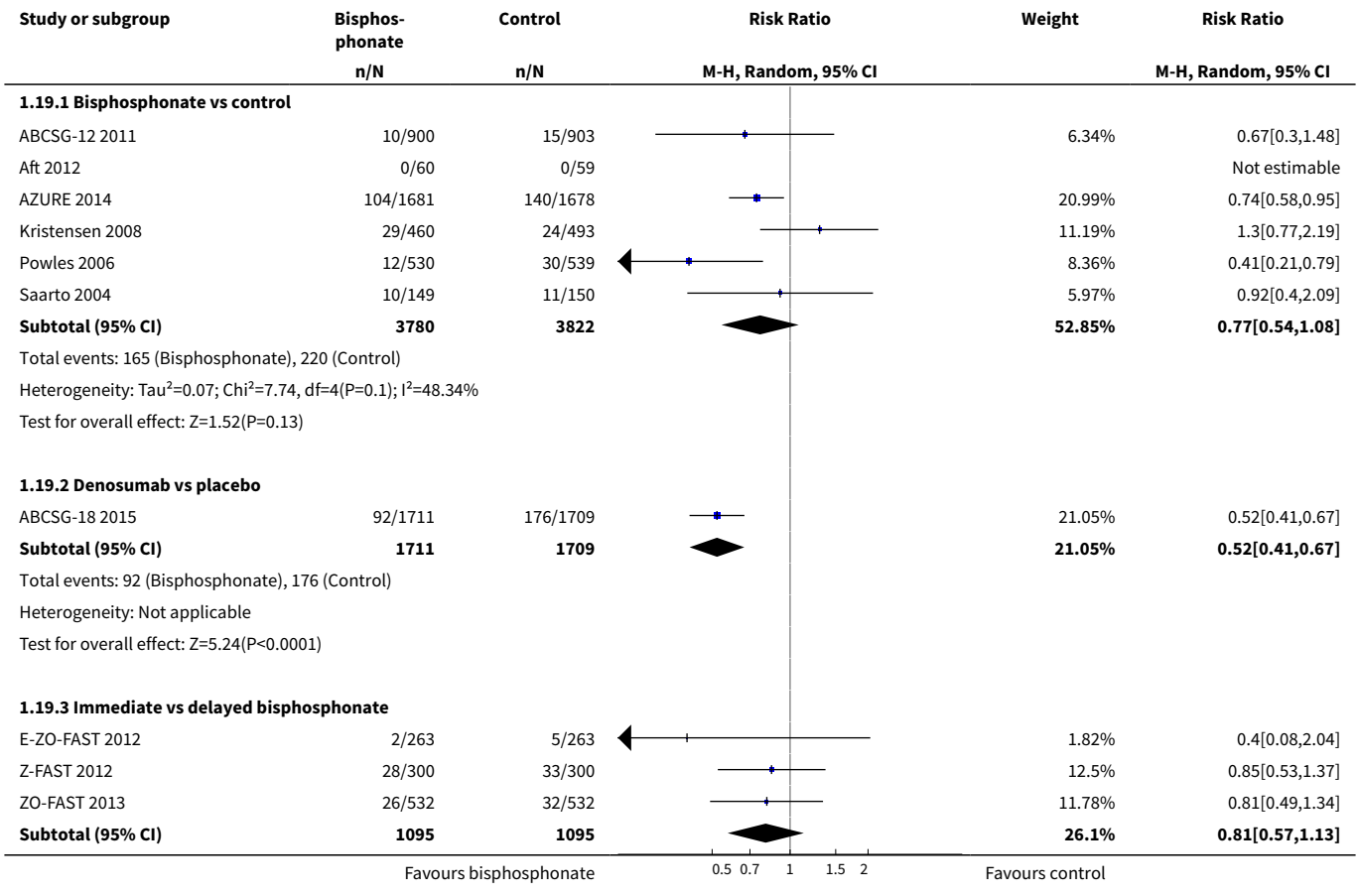
Study or subgroup	Bisphos-phonate n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.18.1 Pre- or perimenopausal					
Aft 2012	20/31	22/33		4%	0.97[0.68,1.38]
AZURE 2014	355/1162	347/1156		13.21%	1.02[0.9,1.15]
GAIN 2013	138/1098	64/533		5.79%	1.05[0.79,1.38]
Kristensen 2008	133/304	120/319		9.21%	1.16[0.96,1.41]
NATAN 2016	43/178	44/183		3.82%	1[0.7,1.45]
Subtotal (95% CI)	**2773**	**2224**		**36.03%**	**1.05[0.96,1.15]**
Total events: 689 (Bisphosphonate), 597 (Control)					
Heterogeneity: Tau²=0; Chi²=1.61, df=4(P=0.81); I²=0%					
Test for overall effect: Z=1.01(P=0.31)					
1.18.2 Postmenopausal					
ABCSG-12 2011	104/900	135/903		7.1%	0.77[0.61,0.98]
Aft 2012	14/29	20/26		2.91%	0.63[0.41,0.97]
AZURE 2014	157/519	190/522		10.13%	0.83[0.7,0.99]
GAIN 2013	131/886	70/463		6.1%	0.98[0.75,1.28]
Kristensen 2008	88/147	91/160		9.28%	1.05[0.87,1.27]
NATAN 2016	39/160	41/157		3.61%	0.93[0.64,1.36]
Z-FAST 2012	23/300	25/300		1.95%	0.92[0.53,1.58]
ZO-FAST 2013	42/532	62/532		3.71%	0.68[0.47,0.98]

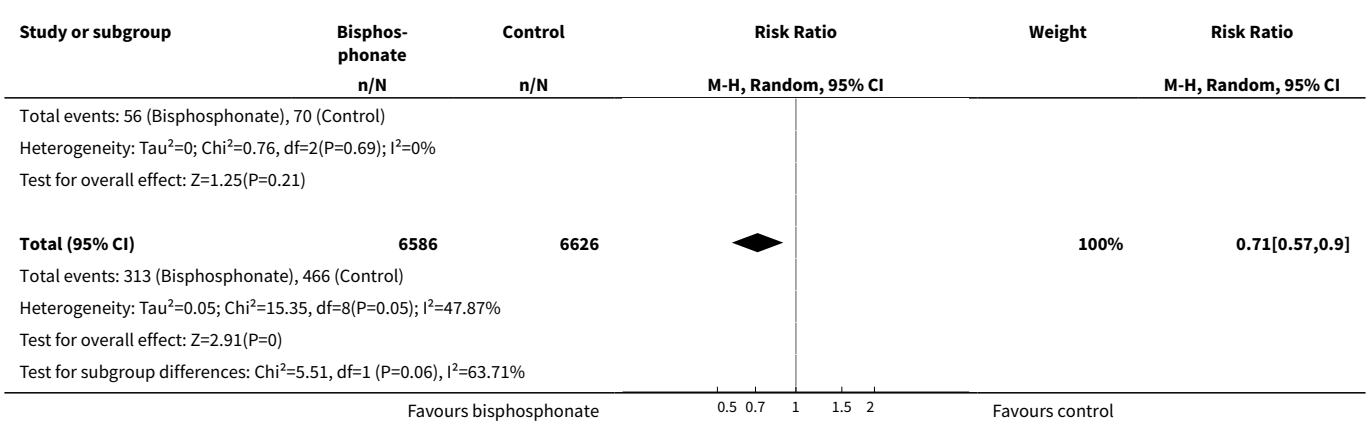


Favours bisphosphonate — Favours control



Analysis 1.19. Comparison 1 Early Breast Cancer (EBC), Outcome 19 Fracture incidence.

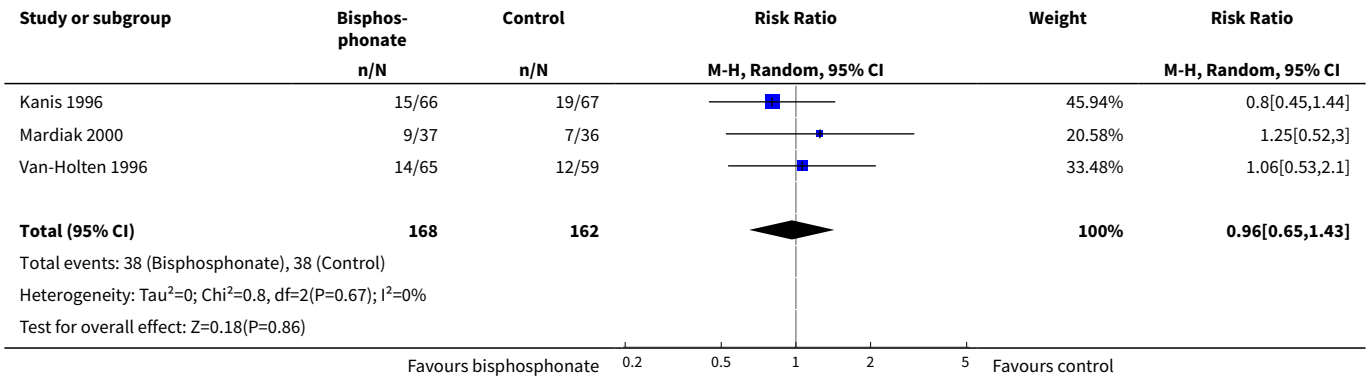




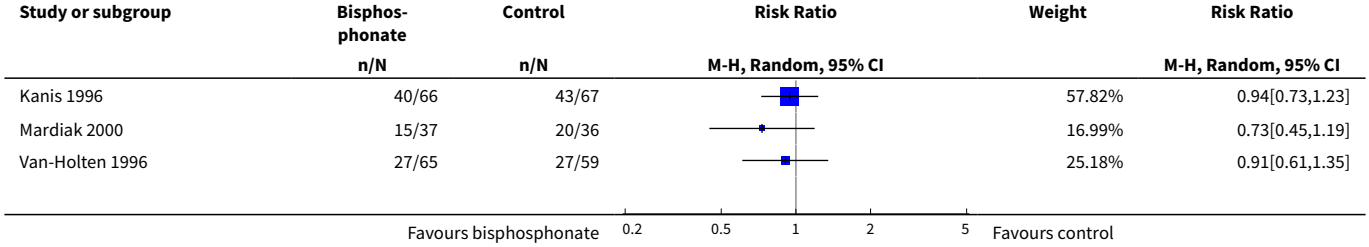
Comparison 2. Advanced Breast Cancer (ABC)

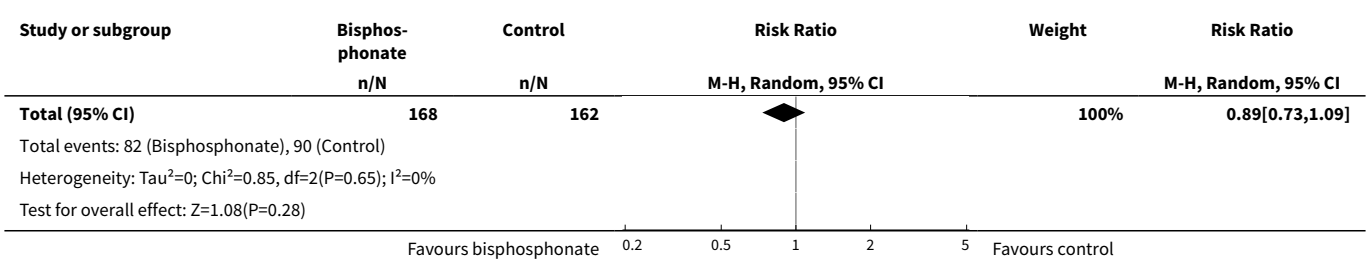
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Bone metastases	3	330	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.65, 1.43]
2 Overall survival	3	330	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.73, 1.09]

Analysis 2.1. Comparison 2 Advanced Breast Cancer (ABC), Outcome 1 Bone metastases.



Analysis 2.2. Comparison 2 Advanced Breast Cancer (ABC), Outcome 2 Overall survival.





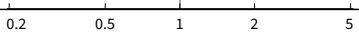
Comparison 3. Breast cancer and bone metastases (BCBM)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SREs: bisphosphonate vs placebo/observation (including hypercalcaemia)	8	2193	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.77, 0.95]
2 SREs: bisphosphonate vs placebo/observation (excluding hypercalcaemia)	9	2810	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.78, 0.95]
3 SREs: by route of administration	11	3219	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.78, 0.91]
3.1 Intravenous bisphosphonates	6	2072	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.73, 0.95]
3.2 Oral bisphosphonates	5	1147	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.76, 0.93]
4 SREs: by bisphosphonate	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Zoledronate 4 mg iv	1	228	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.43, 0.82]
4.2 Pamidronate 90 mg iv	1	754	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.69, 0.88]
4.3 Ibandronate 6 mg iv	2	462	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.67, 0.96]
4.4 Clodronate 1600 mg oral	3	422	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.71, 0.96]
4.5 Ibandronate 50 mg oral	1	564	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.73, 1.02]
4.6 Pamidronate 300 mg oral	1	161	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.70, 1.05]
5 SREs: denosumab vs bisphosphonate	3	2345	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.72, 0.85]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 SREs: standard vs reduced frequency bone-targeted agent	3	901	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.72, 1.26]
7 Median time to SRE	9	2891	Median Ratio (Fixed, 95% CI)	1.43 [1.29, 1.58]
7.1 Bisphosphonate vs placebo/observation	9	2891	Median Ratio (Fixed, 95% CI)	1.43 [1.29, 1.58]
8 Overall survival	7	1935	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.91, 1.11]
8.1 Intravenous bisphosphonate vs placebo/observation	3	1329	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.90, 1.16]
8.2 Oral bisphosphonate vs placebo/observation	4	606	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.71, 1.33]

Analysis 3.1. Comparison 3 Breast cancer and bone metastases (BCBM), Outcome 1 SREs: bisphosphonate vs placebo/observation (including hypercalcaemia).

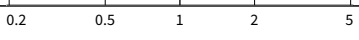
Study or subgroup	Bisphosphonate n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
AREDIA 1998	195/367	263/387		19.33%	0.78[0.69,0.88]
Conte 1996	72/116	69/108		13.23%	0.97[0.79,1.19]
Hultborn 1999	156/201	163/203		20.68%	0.97[0.87,1.07]
Kohno 2005	35/114	59/114		7.35%	0.59[0.43,0.82]
Kristensen 1999	14/49	21/51		3.2%	0.69[0.4,1.2]
Paterson 1993	55/90	70/95		13.04%	0.83[0.68,1.02]
Tubiana-Hulin 2001	42/69	45/68		10.26%	0.92[0.71,1.19]
Van-Holten 1987	52/81	60/80		12.91%	0.86[0.7,1.05]
Total (95% CI)	**1087**	**1106**		**100%**	**0.85[0.77,0.95]**
Total events: 621 (Bisphosphonate), 750 (Control)					
Heterogeneity: Tau^2=0.01; Chi^2=16.05, df=7(P=0.02); I^2=56.39%					
Test for overall effect: Z=3.01(P=0)					



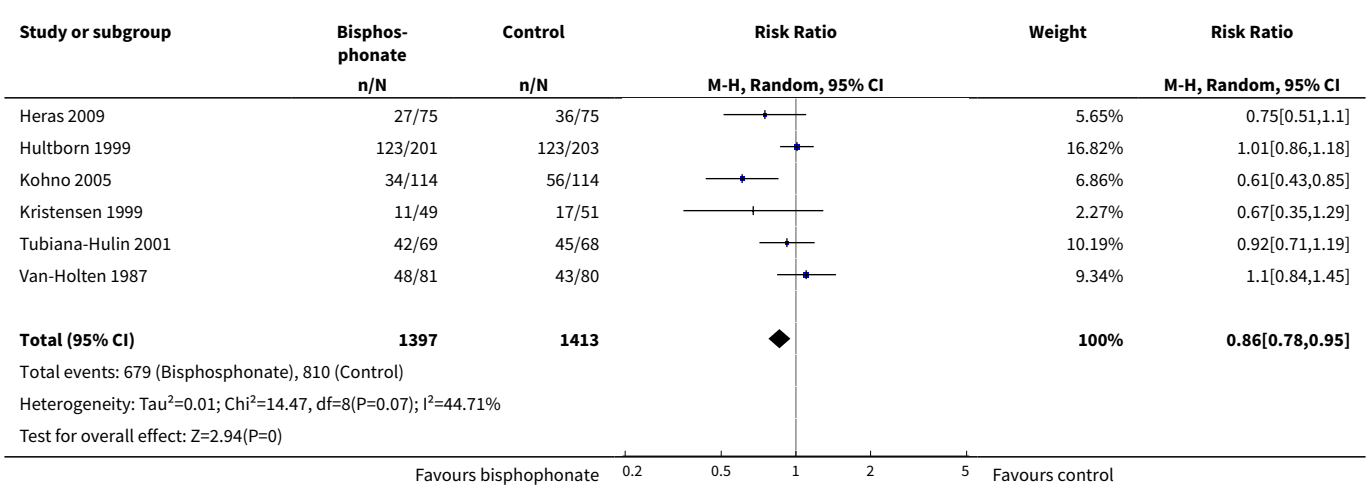
Favours bisphosphonate — Favours control

Analysis 3.2. Comparison 3 Breast cancer and bone metastases (BCBM), Outcome 2 SREs: bisphosphonate vs placebo/observation (excluding hypercalcaemia).

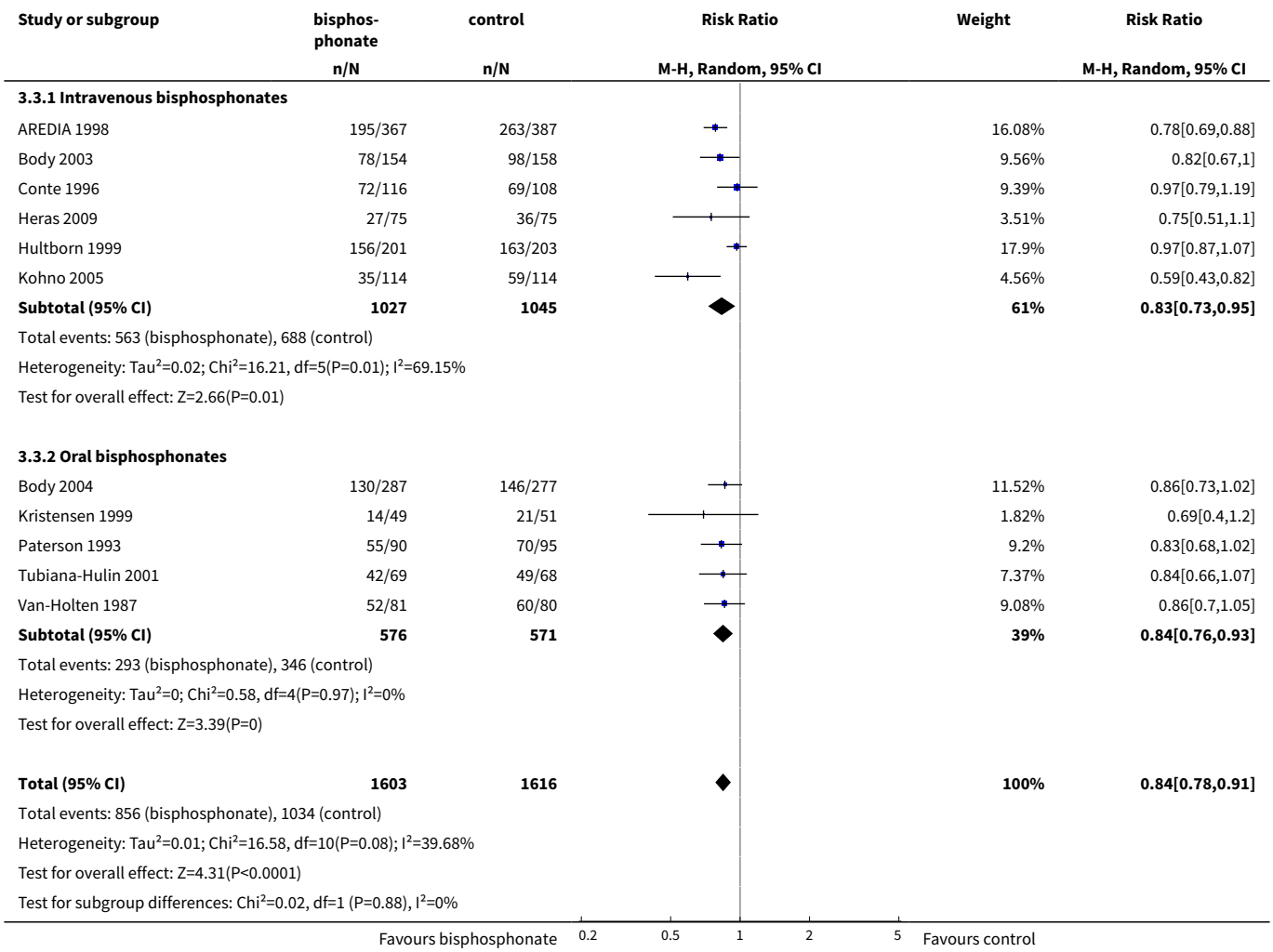
Study or subgroup	Bisphosphonate n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
AREDIA 1998	186/367	246/387		19.53%	0.8[0.7,0.9]
Body 2003	78/154	98/158		13.58%	0.82[0.67,1]
Body 2004	130/287	146/277		15.76%	0.86[0.73,1.02]



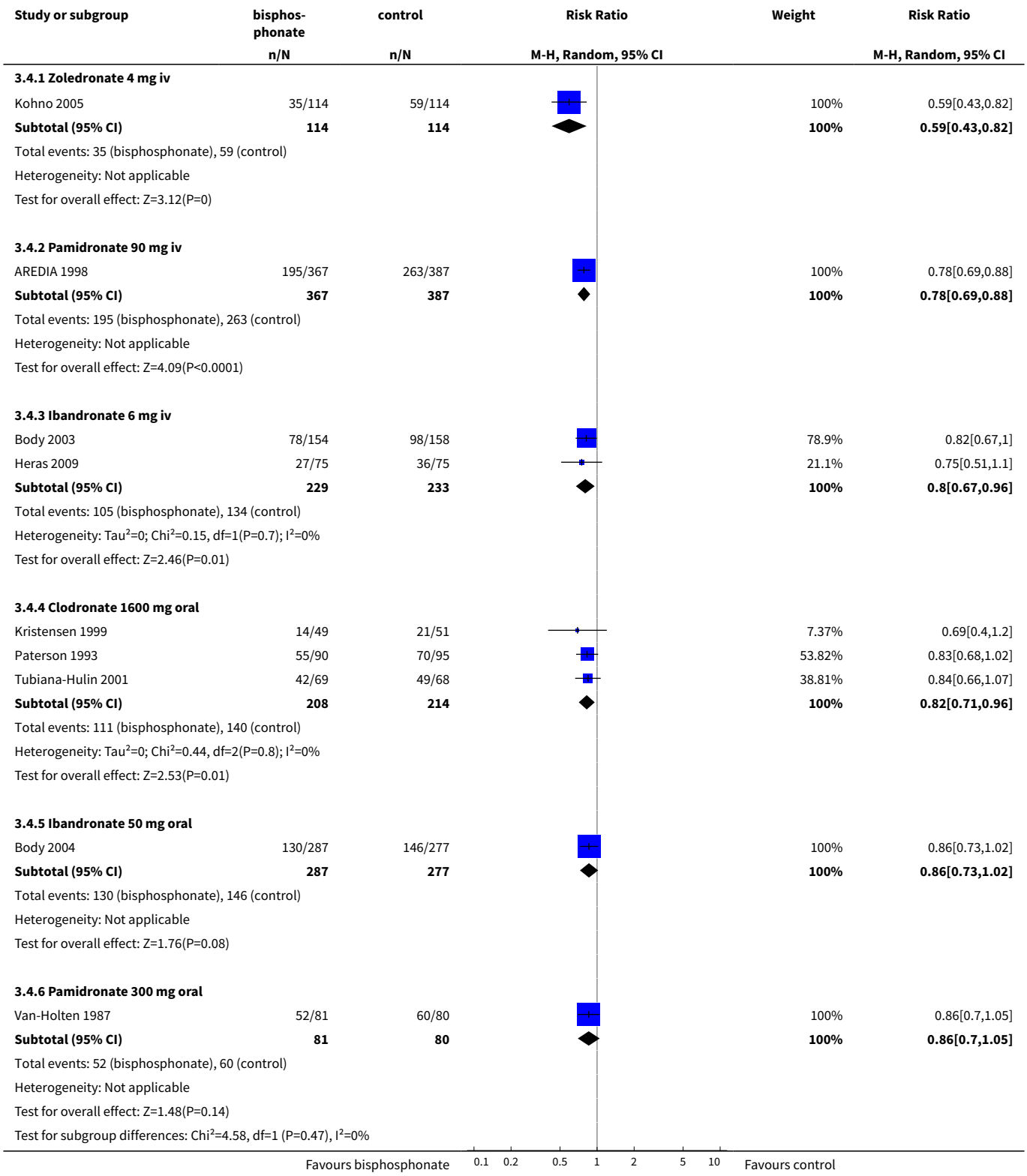
Favours bisphophonate — Favours control



Analysis 3.3. Comparison 3 Breast cancer and bone metastases (BCBM), Outcome 3 SREs: by route of administration.

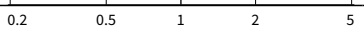


Analysis 3.4. Comparison 3 Breast cancer and bone metastases (BCBM), Outcome 4 SREs: by bisphosphonate.



Analysis 3.5. Comparison 3 Breast cancer and bone metastases (BCBM), Outcome 5 SREs: denosumab vs bisphosphonate.

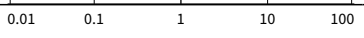
Study or subgroup	Denosumab n/N	Bisphosphonate n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Stopeck 2010	491/1026	623/1020		98.63%	0.78[0.72,0.85]
Lipton 2008	25/212	7/43		1.07%	0.72[0.33,1.57]
Fizazi 2009	3/29	3/15		0.29%	0.52[0.12,2.26]
Total (95% CI)	**1267**	**1078**		**100%**	**0.78[0.72,0.85]**
Total events: 519 (Denosumab), 633 (Bisphosphonate)					
Heterogeneity: Tau^2=0; Chi^2=0.34, df=2(P=0.84); I^2=0%					
Test for overall effect: Z=6.03(P<0.0001)					



Favours denosumab — Favours bisphosphonate

Analysis 3.6. Comparison 3 Breast cancer and bone metastases (BCBM), Outcome 6 SREs: standard vs reduced frequency bone-targeted agent.

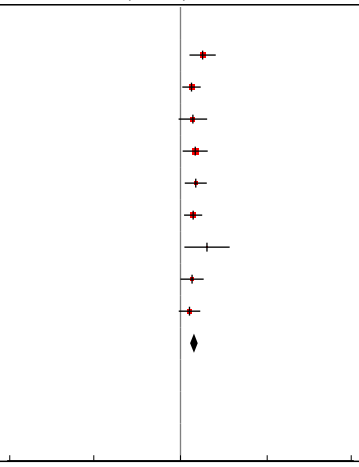
Study or subgroup	Standard freq. n/N	Reduced freq. n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Fizazi 2009	2/38	4/35		5.06%	0.46[0.09,2.36]
OPTIMIZE-2 2014	44/200	47/203		56.67%	0.95[0.66,1.36]
ZOOM 2013	33/216	31/209		38.28%	1.03[0.66,1.62]
Total (95% CI)	**454**	**447**		**100%**	**0.96[0.72,1.26]**
Total events: 79 (Standard freq.), 82 (Reduced freq.)					
Heterogeneity: Tau^2=0; Chi^2=0.87, df=2(P=0.65); I^2=0%					
Test for overall effect: Z=0.32(P=0.75)					



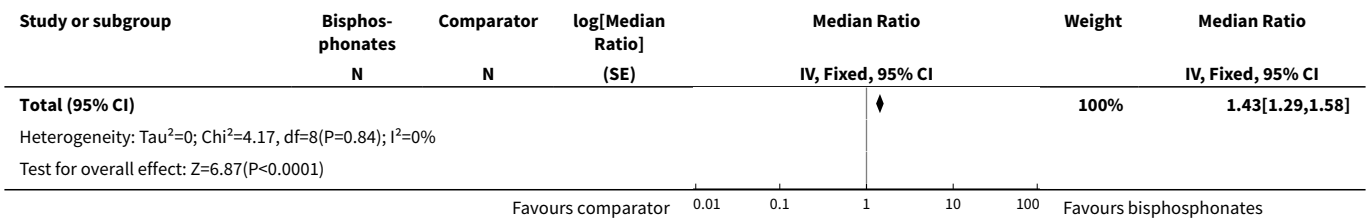
Favours standard freq. — Favours reduced freq.

Analysis 3.7. Comparison 3 Breast cancer and bone metastases (BCBM), Outcome 7 Median time to SRE.

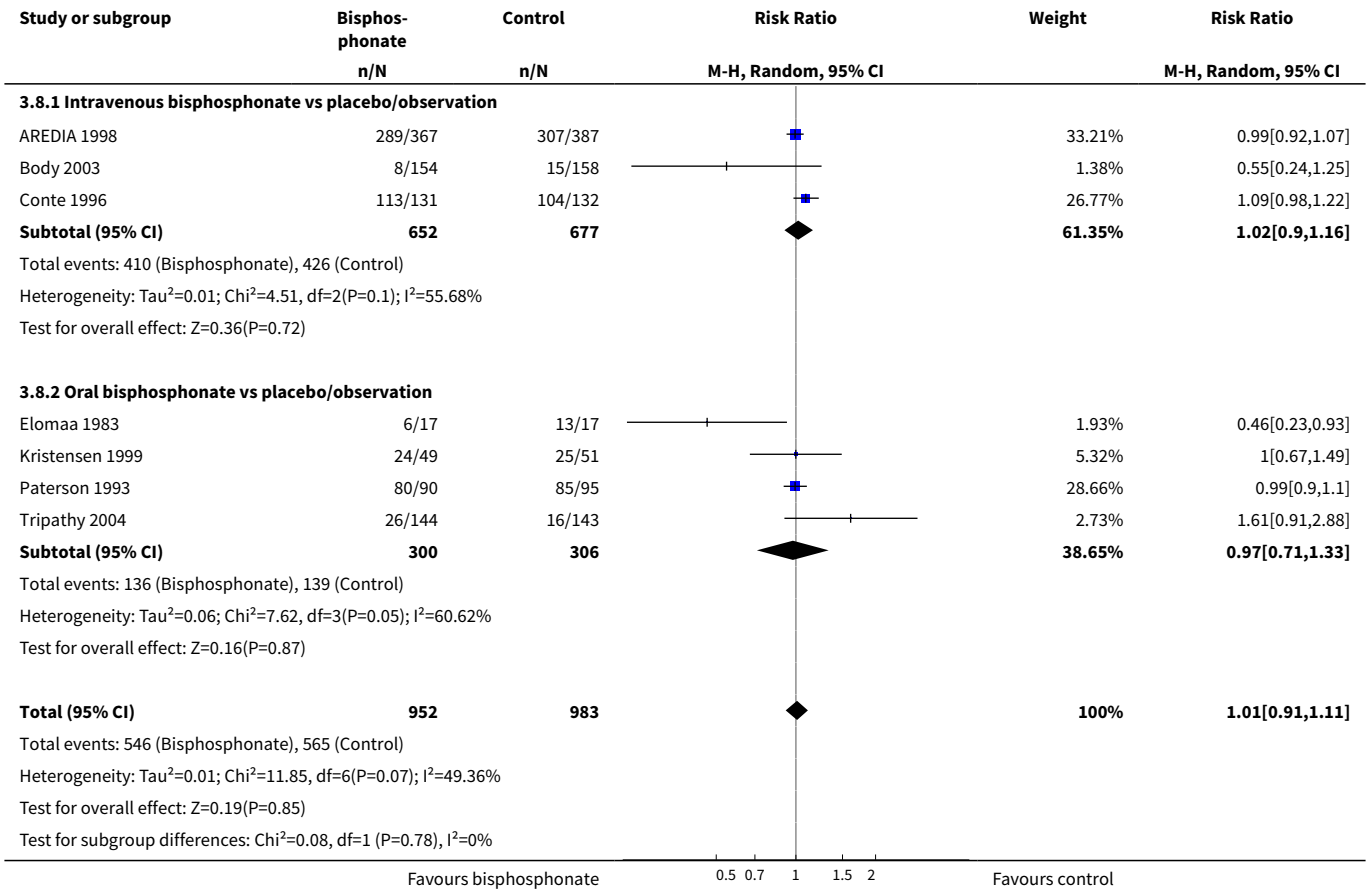
Study or subgroup	Bisphosphonates N	Comparator N	log[Median Ratio] (SE)	Median Ratio IV, Fixed, 95% CI	Weight	Median Ratio IV, Fixed, 95% CI
3.7.1 Bisphosphosphonate vs placebo/observation						
AREDIA 1998	367	387	0.6 (0.179)		8.52%	1.8[1.27,2.55]
Body 2003	154	158	0.3 (0.124)		17.75%	1.34[1.05,1.71]
Body 2004	287	277	0.3 (0.194)		7.25%	1.39[0.95,2.03]
Conte 1996	116	108	0.4 (0.169)		9.57%	1.48[1.06,2.06]
Heras 2009	75	75	0.4 (0.15)		12.03%	1.5[1.12,2.01]
Hultborn 1999	201	203	0.3 (0.123)		18.1%	1.4[1.1,1.78]
Paterson 1993	90	95	0.7 (0.307)		2.88%	2.02[1.11,3.69]
Tubiana-Hulin 2001	69	68	0.3 (0.157)		11.04%	1.36[1,1.85]
Van-Holten 1987	81	80	0.2 (0.145)		12.87%	1.27[0.96,1.69]
Subtotal (95% CI)					**100%**	**1.43[1.29,1.58]**
Heterogeneity: Tau^2=0; Chi^2=4.17, df=8(P=0.84); I^2=0%						
Test for overall effect: Z=6.87(P<0.0001)						



Favours comparator — Favours bisphosphonates



Analysis 3.8. Comparison 3 Breast cancer and bone metastases (BCBM), Outcome 8 Overall survival.



ADDITIONAL TABLES

Table 1. Early breast cancer: baseline characteristics

Study	Treatment vs comparator	Age: mean & SD[a]	Menopausal status	ER status	Chemotherapy	Endocrine therapy
ABCSG-12 2011	Zoledronate vs observation	Bisphosphonate: < 40 years: 18% > 40 years: 82% Observation:	Premenopausal when recruited	ER-positive: Bisphosphonate: 93% Control: 94%	**Preoperative chemotherapy**	NR

Table 1. Early breast cancer: baseline characteristics *(Continued)*

		< 40 years: 19% > 40 years: 81%			Bisphosphonate: 6% Control: 5%	
ABCSG-18 2015	Denosumab vs placebo	Denosumab: < 60 years: 30% > 60 years: 70% Placebo: < 60 years: 28% > 60 years: 72%	Postmenopausal only	ER-positive: Bisphosphonate: 99% Control: 100%	**Neo/adjuvant therapy:** Bisphosphonate: 25% Control: 25%	**Endocrine therapy before randomisation:** Bisphosphonate: 84% Control: 85%
Aft 2012	Zoledronate vs observation	Bisphosphonate: mean 50 (range 30-68) years Observation: mean 49.1 (range 32-69) years	**Premenopausal** Bisphosphonate: 52% Control: 56% **Postmenopausal:** Bisphosphonate: 48% Control: 44%	ER-positive: Bisphosphonate: 53% Control: 58%	NR	NR
AZURE 2014	Zoledronate vs observation	Bisphosphonate: 51.6 ± 9.9 years Observation: 51.3 ± 10 years	**Premenopausal:** Bisphosphonate: 45% Control: 45% **Postmenopausal:** Bisphosphonate: 45% Control: 46%	ER-positive: Bisphosphonate: 78% Control: 78%	**Intended treatment chemotherapy plan:** Bisphosphonate: 22% Control: 21%	**Intended treatment endocrine therapy plan:** Bisphosphonate: 5% Control: 5%
Diel 1998	Clodronate vs observation	Across both groups: Median 51 (range: 24-78) years	**Postmenopausal:** Bisphosphonate: 64% Control: 61%	ER-positive: Bisphosphonate: 66% Control: 58%	**Adjuvant chemotherapy:** Bisphosphonate: 25% Control: 28%	**Adjuvant endocrine therapy:** Bisphosphonate: 31% Control: 30%
GAIN 2013	Ibandronate vs observation	Bisphosphonate: < 60 years: 83% > 60 years: 17% Observation: < 60 years: 81% > 60 years: 19%	**Premenopausal:** Bisphosphonate: 48% Control: 47% **Postmenopausal:** Bisphosphonate: 51% Control: 53%	Hormone receptor-positive: Bisphosphonate: 77% Control: 78%	NR	**Adjuvant therapy:** Bisphosphonate: 66% Control: 65%

Table 1. Early breast cancer: baseline characteristics *(Continued)*

Hershman 2008	Zoledronate vs placebo	Bisphosphonate: 43 ± 6 years Placebo: 42 ± 6 years	Premenopausal only	Hormone receptor-positive: Bisphosphonate: 74% Control: 70%	Bisphosphonates: 4 cycles: 18%; 6 to 8 cycles: 78% Control: 4 cycles: 19%; 6 to 8 cycles: 81%	**Endocrine therapy after treatment:** Bisphosphonates: 70% Control: 70%
Kristensen 2008	Pamidronate vs observation	Bisphosphonate: < 39 years: 16% 40-49 years: 45% 50-59 years: 23% 60-69 years: 15% Observation: < 39 years: 15% 40-49 years: 48% 50-59 years: 23% 60-69 years: 14%	**Premenopausal:** Bisphosphonate: 67% Control: 66% **Postmenopausal:** Bisphosphonate: 33% Control: 34%	ER-positive: Bisphosphonate: 14% Control: 17%	NR	NR
NATAN 2016	Zoledronate vs observation	Bisphosphonate: < 55 years: 67% > 55 years: 33% Observation: < 55 years: 66% > 55 years: 34%	**Premenopausal:** Bisphosphonate: 22% Control: 25%	ER-positive and/or PR-positive: Bisphosphonate: 78% Control: 78%	NR	NR
NSABP-34 2012	Clodronate vs placebo	Bisphosphonate: < 49 years: 36% > 50 years: 64% Placebo: < 49 years: 36% > 50 years: 65%	NR	ER-positive and/or PR-positive: Bisphosphonate: 78% Control: 78%	Bisphosphonate: 21% Control: 21%	Bisphosphonate: 31% Control: 31%
Powles 2006	Clodronate vs placebo	Bisphosphonate: 52.8 ± 6 years Placebo: 52.7 ± 10.5 years	**Premenopausal:** Bisphosphonate: 50% Control: 49% **Postmenopausal:** Bisphosphonate: 50%	ER-positive: Bisphosphonate: 46% Control: 45%	Bisphosphonate: 16% Control: 15%	Tamoxifen: Bisphosphonate: 32% Control: 29%

Table 1. Early breast cancer: baseline characteristics *(Continued)*

			Control: 51%			
Saarto 2004	Clodronate vs observation	Bisphosphonate: 52 years (no SD provided) Observation: 52 years (no SD provided)	**Premenopausal:** Bisphosphonate: 48% Control: 57% **Postmenopausal:** Bisphosphonate: 52% Control: 43%	ER-positive: Bisphosphonate: 61% Control: 68%	Bisphosphonate: 50% Control: 58%	**Pretreatment antioestrogen:** Bisphosphonate: 50% Control: 58%
SWOG-S0307 2015	Zoledronate vs clodronate vs ibandronate	Median 53 years (range not provided)	Postmenopausal or aged 50 plus: 58% (not reported by group)	ER-positive: 77% of tumours (not reported by group)	Planned adjuvant chemotherapy: 80% (not reported by group)	Planned endocrine therapy: 76% (not reported by group)
Tevaarwerk 2007	Zoledronate vs observation	Across both groups: All women older than 60 years	Postmenopausal only	ER-positive: Bisphosphonate: 81% Control: 91%	**Any adjuvant chemotherapy:** Bisphosphonate: 92% Control: 97%	**Tamoxifen, other SERM or AI:** Bisphosphonate: 75% Control: 72%
E-ZO-FAST 2012	Immediate vs delayed zoledronate	Immediate: median 58 (range 40-81) years Delayed: median 58 (range 44-81) years	Postmenopausal only	NR	**Prior chemotherapy** Immediate: 52% Delayed: 53%	NR
Z-FAST 2012	Immediate vs delayed zoledronate	Immediate: 61.4 ± 9.28 years Delayed: 61.0 ± 8.92 years	Postmenopausal only	NR	NR	NR
ZO-FAST 2013	Immediate vs delayed zoledronate	Immediate: median 57 (range 36-87) years Delayed: median 58 (range 37-81) years	Postmenopausal only	NR	**Prior adjuvant therapy** Immediate: 54% Delayed: 53%	NR

AI: aromatase inhibitor; **ER**: oestrogen receptor; **NR**: not reported; **PR**: progesterone receptor; **SD**: standard deviation; **SERM**: selective estrogen receptor modulator

[a]Unless otherwise stated.

Table 2. Early breast cancer: toxicity - osteonecrosis of the jaw, hypocalcaemia, renal dysfunction & drug-related death

Study	Treatment vs comparator	ONJ		Hypocalcaemia		Renal dysfunction		Drug-related death	
		Bone agent (n/N)	Comparator (n/N)	Bone agent (n/N)	Comparator (n/N)	Bone agent (n/N)	Comparator (n/N)	Bone agent (n/N)	Comparator (n/N)
ABCSG-12 2011	Zoledronate vs observation	0/899	0/904	NR	NR	0/899	0/904	0/899	0/904
ABCSG-18 2015[a]	Denosumab vs placebo	0/1709	0/1690	1/1709	3/1690	2[a]/1709	3[a]/1690	1/1709	0/1690
Aft 2012	Zoledronate vs observation	1/60	0/59	NR	NR	0/60	0/59	NR	NR
AZURE 2014	Zoledronate vs observation	26/1685	0/1667	NR	NR	188/1685	158/1667	0/1685	0/1667
Diel 1998	Clodronate vs observation	NR	NR	NR	NR	NR	NR	NR	NR
GAIN 2013	Ibandronate vs observation	2/1832	0/968	NR	NR	NR	NR	0/1832	0/968
Hershman 2008	Zoledronate vs placebo	0/50	0/53	NR	NR	0/50	0/53	NR	NR
Kristensen 2008	Pamidronate vs observation	NR	NR	NR	NR	NR	NR	NR	NR
NATAN 2016	Zoledronate vs observation	5/343	0/350	NR	NR	7[b]/343	4[b]/350	0/343	0/350
NSABP-34 2012	Clodronate vs placebo	1/1612	0/1623	1/1612 (G3)	2/1523 (G3/4)	NR	NR	4/1612	7/1623
Powles 2006	Clodronate vs placebo	0/530	0/539	NR	NR	28/530	31/539	0/530	0/539
Saarto 2004	Clodronate vs observation	NR	NR	NR	NR	NR	NR	NR	NR
SWOG-S0307 2015	Zoledronate vs clodronate vs ibandronate	Zoledronate: 24/2094	Clodronate: 6/2151 Ibandronate: 10/1507	NR	NR	NR	NR	NR	NR
Tevaarwerk 2007	Zoledronate vs observation	0/36	0/32	0[c]/36	0[c]/32	NR	NR	NR	NR
E-ZO-FAST 2012[d]	Immediate vs delayed zoledronate	2/252	0/270	NR	NR	1/252	0/270	0/252	0/270

Table 2. Early breast cancer: toxicity - osteonecrosis of the jaw, hypocalcaemia, renal dysfunction & drug-related death *(Continued)*

Z-FAST 2012[d]	Immediate vs delayed zoledronate	0/300	0/300	NR	NR	5/300 (G1 to 4)	4/300 (G1 to 4)	0/300	0/300
ZO-FAST 2013[d]	Immediate vs delayed zoledronate	2/524	0/536	NR	NR	3/524 (G1/2)	2/536 (G1/2)	0/524	0/536

G: grade; **n**: number of events; **N**: number of women studied in each group; **NR**: not reported; **ONJ**: osteonecrosis of the jaw
[a]Number of events for renal dysfunction refers to renal failure.
[b]Any grade.
[c]"No clinically significant changes in calcium" (Tevaarwerk 2007).
[d]Control arm was delayed zoledronate.

Table 3. Early breast cancer: toxicity - nausea, fatigue, fever & influenza symptoms

Study	Treatment vs comparator	Nausea		Fatigue		Fever		Influenza-type symptoms	
		Bone agent (n/N)	Comparator (n/N)	Bone agent (n/N)	Comparator (n/N)	Bone agent (n/N)	Comparator (n/N)	Bone agent (n/N)	Comparator (n/N)
ABCSG-12 2011	Zoledronate vs observation	79/899	55/904	192/899	169/904	85/899	21/904	NR	NR
ABCSG-18 2015	Denosumab vs placebo	49/1709	42/1690	108/1709	98/1690	13/1709	8/1690	25/1709	20/1690
Aft 2012	Zoledronate vs observation	NR	NR	NR	NR	3/60	2/59	NR	NR
AZURE 2014	Zoledronate vs observation	NR	NR	NR	NR	37/1685	24/1667	NR	NR
Diel 1998	Clodronate vs observation	NR	NR	NR	NR	NR	NR	NR	NR
GAIN 2013	Ibandronate vs observation	NR	NR	NR	NR	NR	NR	NR	NR
Hershman 2008	Zoledronate vs placebo	NR	NR	24/50	29/53	11/50	10/53	21/50	21/53
Kristensen 2008	Pamidronate vs observation	324[a]/460	337[a]/493	NR	NR	NR	NR	NR	NR
NATAN 2016	Zoledronate vs observation	NR	NR	65[b]/343	36[b]/350	28[b]/343	1[b]/350	NR	NR
NSABP-34 2012	Clodronate vs placebo	NR	NR	NR	NR	NR	NR	NR	NR

Table 3. Early breast cancer: toxicity - nausea, fatigue, fever & influenza symptoms *(Continued)*

Powles 2006	Clodronate vs placebo	143/530	161/539	NR	NR	NR	NR	NR	NR
Saarto 2004	Clodronate vs observation	NR	NR	NR	NR	NR	NR	NR	NR
SWOG-S0307 2015	Zoledronate vs clodronate vs ibandronate	NR	NR	NR	NR	NR	NR	NR	NR
Tevaarwerk 2007	Zoledronate vs observation	NR	NR	NR	NR	NR	NR	NR	NR
E-ZO-FAST 2012[c]	Immediate vs delated zoledronate	17/252	14/270	38/252	50/270	17/252	0/270	15/252	3/270
Z-FAST 2012[c]	Immediate vs delated zoledronate	41/300	40/300	101/300	88/300	27/300	6/300	NR	NR
ZO-FAST 2013[c]	Immediate vs delated zoledronate	46/524	42/536	84/524	81/536	78/524	15/536	45/524	8/536

n: number of events; **N**: number of women studied in each group; **NR**: not reported

[a]Nausea and vomited reported together.

[b]Any grade.

[c]Control arm was delayed zoledronate.

Table 4. Advanced breast cancer: skeletal-related event expressed as a risk ratio

Study	Treatment	Comparator	Number of skeletal-related events		Ratio: Bisphosphonate/comparator	P value reported
			Bisphosphonate	Comparator		
Kanis 1996 (N = 133)	Clodronate 1600 mg oral	Placebo	71 Event rate = event/100 patient years	96.5	0.74	P < 0.01
Mardiak 2000 (N = 73)	Clodronate 1600 mg oral	Placebo	NR	NR	NR	NR
Van-Holten 1996 (N = 124)	Pamidronate 300 mg oral	Control	NR	NR	NR	NR

N: total number of women in the study; **NR**: not reported

Table 5. Advanced breast cancer: median time to skeletal-related event

Study	Treatment	Comparator	Median time to event (months)		Ratio - Bisphosphonate/Comparator	P value reported
			Bisphosphonate	Comparator		
Kanis 1996 (N = 133)	Clodronate 1600 mg oral	Placebo	NR Reported no. of people "event free"	NR	NR	No significant difference
Mardiak 2000 (N = 73)	Clodronate 1600 mg oral	Placebo	28.4	13.4	2.1	P = 0.42
Van-Holten 1996 (N = 124)	Pamidronate 300 mg oral	Control	Not reached. First bone event was not within the first 36 months of the analysis	Not reached	-	-

N: total number of women in the study; **NR**: not reported

Table 6. Advanced breast cancer: median survival time

Study	Treatment	Comparator	Median survival time (months)		Ratio - Bisphosphonate/comparator	P value reported
			Bisphosphonate	Comparator		
Kanis 1996 (N = 133)	Clodronate 1600 mg oral	Placebo	NR Reported no. of events in each group	NR	NR	Not significantly different
Mardiak 2000 (N = 73)	Clodronate 1600 mg oral	Placebo	59.4	54.7	1.09	P = 0.35

Table 6. Advanced breast cancer: median survival time *(Continued)*

Van-Holten 1996 (N = 124)	Pamidronate 300 mg oral	Control	NR	NR	NR	P = 0.30

N: total number of women in the study; **NR**: not reported

Table 7. Advanced breast cancer: quality of life

Study	Questionnaires used	Summary of findings
Kanis 1996	NR	NR
Mardiak 2000	NR	NR
Van-Holten 1996	Participants scored questionnaire items on a 4-point scale (0 = none, 3 = very severe)	At baseline, mean scores were similar across the 2 groups however pamidronate had a worse score for fatigue compared to control. At follow-up, the mean scores were similar in the 2 groups with similar worsening over time in mobility and gastrointestinal toxicity. There was no change in bone pain and fatigue over time or between the 2 groups

NR: not reported

Table 8. Advanced breast cancer: toxicity - osteonecrosis of the jaw, renal dysfunction, bone pain, drug-related death

Study	Treatment vs comparator	Osteonecrosis of the jaw		Renal dysfunction		Bone pain		Drug-related death		Additional comment
		Bone agent (n/N)	Comparator (n/N)	Bone agent (n/N)	Comparator (n/N)	Bone agent (n/N)	Comparator (n/N)	Bone agent (n/N)	Comparator (n/N)	
Kanis 1996	Clodronate 1600 mg oral vs placebo	NR	NR	NR	NR	13[a]/66	17[a]/67	NR	NR	No hypocalcaemia observed in either group
Mardiak 2000	Clodronate 1600 mg oral vs placebo	NR	NR	NR	NR	NR	NR	NR	NR	1 participant with rash (clodronate); 2 participants with gastrointestinal toxicity (1 clodronate, 1 placebo); 1 participant with abdominal pain (placebo)
Van-Holten 1996	Pamidronate 300 mg oral vs control	NR	NR	NR	NR	"...did not change over time and there was no effect of pamidronate treatment"		NR	NR	4 participants with gastrointestinal intolerance in pamidronate group

n: number of events; **N**: number of women studied in each group; **NR**: not reported
[a]Received radiotherapy for bone pain.

Table 9. Advanced breast cancer: toxicity - nausea, fatigue, fever & influenza symptoms

Study	Treatment vs comparator	Nausea		Fatigue		Fever		Influenza-type symptoms	
		Bone agent (n/N)	Comparator (n/N)	Bone agent (n/N)	Comparator (n/N)	Bone agent (n/N)	Comparator (n/N)	Bone agent (n/N)	Comparator (n/N)
Kanis 1996	Clodronate 1600 mg oral vs placebo	NR	NR	NR	NR	NR	NR	NR	NR
Mardiak 2000	Clodronate 1600 mg oral vs placebo	NR	NR	NR	NR	NR	NR	NR	NR
Van-Holten 1996	Pamidronate 300 mg oral vs control	NR	NR	Scored 0.6 (worse than control arm)	Scored 0.3	NR	NR	NR	NR

n: number of events; **N**: number of women studied in each group; **NR**: not reported

Table 10. Breast cancer with bone metastases: skeletal-related event rate

Study	Bisphosphonate	Comparator	No. of skeletal-related events		Ratio: Bisphosphonate/comparator	P value reported
			Bisphosphonate	Comparator		
Bisphosphonate vs placebo/open						
AREDIA 1998 (N = 751)	Pamidronate 90 mg iv	Placebo	2.4 Event rate = mean no. of events/year	3.7	0.65	< 0.001
Body 2003 (N = 312)	Ibandronate 6 mg iv	Placebo	0.56 Event rate = events/patient year	1.08	0.52	0.03
Body 2004 (N = 564)	Ibandronate 50 mg oral	Placebo	0.99 Rate assessed using SMPR; pooled results of 50 mg ibandronate versus placebo from studies MF4434 and MF4414	1.15	0.86	0.041
Conte 1996 (N = 224)	Pamidronate 45 mg iv	Open	135 Event rate = total events per arm	169	0.80	-
Elomaa 1983 (N = 34)	Clodronate 1600 mg oral	Placebo	NR	NR	NR	NR
Heras 2009 (N = 150)	Ibandronate 6 mg iv	Placebo	NR	NR	NR	NR
Hultborn 1999 (N = 404)	Pamidronate 60 mg iv	Placebo	0.98 Event rate = cumulative events/follow-up	1.41	0.70	< 0.01
Kohno 2005 (N = 227)	Zoledronate 4 mg iv	Placebo	0.63 Event rate = events per year	1.10	0.57	0.016
Kristensen 1999 (N = 100)	Clodronate 800 mg oral, 2/d for 2 years	Open	0.4 Event rate = cumulative proportion of skeletal events	0.5	0.8	-
Martoni 1991 (N = 38)	Clodronate 300 mg oral	Placebo	NR	NR	NR	NR
Paterson 1993 (N = 173)	Clodronate 800 mg oral, 2/d for up to 3 years	Placebo	218.6 Event rate = cumulative proportion of skeletal events per 100 patient-years	304.8	0.72	P < 0.001
Tripathy 2004 (N = 287)	Ibandronate 50 mg oral	Placebo	0.98 Rate assessed using SMPR; refers only to the results of	1.2	0.81	0.037

Table 10. Breast cancer with bone metastases: skeletal-related event rate *(Continued)*

			the 50 mg ibandronate arm versus placebo within study MF4434			
Tubiana-Hulin 2001 (N = 144)	Clodronate 1600 mg oral	Placebo	NR "No difference between groups"	NR	NR	NR
Van-Holten 1987 (N = 161)	Pamidronate 150 mg oral, 2/d indefinitely	Open	90 Event rate = total number of events. Events = "complications"	144	0.63	0.003
Direct comparisons of different bisphosphonate regimens						
Diel 1999 (N = 318)	Pamidronate 60 mg iv	Clodronate 2400 mg oral or 900 mg iv	16 Event = number of people with fractures	Clodronate oral = 11 Clodronate iv = 19 Event = number of people with fractures	NR	NR
Rosen 2004 (N = 1130)	Zoledronate 4 mg iv	Pamidronate 90 mg iv	NR	NR	0.81	0.037
von Au 2016 (N = 375)	Pamidronate 60 mg iv	Clodronate 900 mg iv every 3 weeks or 2400 mg/d oral	7.3% Event rate = fracture rate	14.3% or 17.3%	NR	0.07 (pamidronate versus clodronate oral)
ZICE 2014 (N = 1404)	Ibandronate 50 mg oral	Zoledronate 4 mg iv	0.507 Event rate = annual rate of SRE	0.425	1.19	0.035
Bone-targeted agents vs bisphosphonate						
Fizazi 2009 (N = 44)	Denosumab 180 mg sc every 4 weeks	Bisphosphonate iv (clinician choice)	NR	NR	NR	NR
Lipton 2008 (N = 255)	Denosumab sc every 4 weeks (30 mg, 120 mg or 180 mg) or every 12 weeks (60 mg or 180 mg)	Bisphosphonate iv (either zoledronate, pamidronate or ibandronate)	NR	NR	NR	NR
Stopeck 2010 (N = 2046)	Denosumab 120 mg sc (iv placebo)	Zoledronate 4 mg iv (sc placebo)	0.58 Event rate assessed using SMPR, defined as the ratio of the number of SREs per participant divided by the participant's time at risk. An exploratory endpoint	0.45	0.78	0.004

Table 10. Breast cancer with bone metastases: skeletal-related event rate *(Continued)*

Standard vs reduced bisphosphonate/bone agent						
CALGB-70604 2015 (N = 820)	Zoledronate 4 mg iv every 4 weeks	Zoledronate 4 mg iv every 12 weeks	NR	NR	NR	NR
Fizazi 2009 (N = 73)	Denosumab 180 mg sc every 4 weeks	Denosumab 180 mg sc every 12 weeks	NR	NR	NR	NR
OPTIMIZE-2 2014 (N = 403)	Zoledronate 4 mg iv every 4 weeks	Zoledronate 4 mg iv every 12 weeks	0.46 Event rate assessed using SMR, defined as the number of events per year	0.50	NR	NR
ZOOM 2013 (N = 425)	Zoledronate 4 mg iv every 4 weeks	Zoledronate 4 mg iv every 12 weeks	0.22 Event rate = skeletal morbidity rate (SRE/patient/year) Non-inferiority not demonstrated	0.26	NR	NR

iv: intravenous; **N**: total number of women in each study; **NR**: not reported; **sc**: subcutaneous; **SMPR**: skeletal morbidity period rate; **SRE**: skeletal related event

Table 11. Breast cancer with bone metastases: median time to skeletal-related event

Study	Bisphosphonate	Comparator	Median time to event (months)		Ratio: bisphosphonate/comparator	P value reported
			Bisphosphonate	Comparator		
Bisphosphonate vs placebo/open						
AREDIA 1998 (N = 751)	Pamidronate 90 mg iv	Placebo	12.7	7	1.81	< 0.001
Body 2003 (N = 312)	Ibandronate 6 mg iv	Placebo	12.65	8.28	1.34	0.018
Body 2004 (N = 564)	Ibandronate 50 mg oral	Placebo	20.8[a]	14.9[a]	1.39	0.089
Conte 1996 (N = 224)	Pamidronate 45 mg iv	Open	8.9	6	1.48	0.02
Elomaa 1983 (N = 34)	Clodronate 1600 mg oral	Placebo	NR	NR	NR	NR
Heras 2009 (N = 150)	Ibandronate 6 mg iv	Placebo	15.2[a]	10.1[a]	1.50	0.007

Table 11. Breast cancer with bone metastases: median time to skeletal-related event *(Continued)*

Hultborn 1999 (N = 404)	Pamidronate 60 mg iv	Placebo	11.8	8.4	1.4	0.006
Kohno 2005 (N = 228)	Zoledronate 4 mg iv	Placebo	NR	12^	NR The median time to first SRE was not reached in the zoledronic acid arm, versus 364 days in the placebo arm	0.007
Kristensen 1999 (N = 100)	Clodronate 800 mg oral, 2/d for 2 years	Open	NR[b]	NR[b]	NR Time to skeletal event delayed with clodronate according to Kaplan-Meier curves	0.015
Martoni 1991 (N = 38)	Clodronate 300 mg oral	Placebo	NR	NR	NR	NR
Paterson 1993 (N = 173)	Clodronate 800 mg oral, 2/d for up to 3 years	Placebo	9.9	4.9	2.02	0.022
Tripathy 2004 (N = 287)	Ibandronate 50 mg oral	Placebo	17.5[a]	11.1[a]	1.58	NS
Tubiana-Hulin 2001 (N = 144)	Clodronate 1600 mg oral	Placebo	8.7	6.4	1.36	0.05
Van-Holten 1987 (N = 161)	Pamidronate 150 mg oral, 2/d indefinitely	Open	14	11	1.27	0.10
Direct comparisons of different bisphosphonate regimens						
Diel 1999 (N = 318)	Pamidronate 60 mg iv	Clodronate 2400 mg oral or 900 mg iv	NR	NR	NR	NR
Rosen 2004 (N = 1130)	Zoledronate 4 mg iv	Pamidronate 90 mg iv	10.3	5.8	0.56	0.013
von Au 2016 (N = 375)	Pamidronate 60 mg iv	Clodronate 900 mg iv every 3 weeks or 2400 mg/d oral	NR	NR	NR	NR
ZICE 2014 (N = 1404)	Ibandronate 50 mg oral	Zoledronate 4 mg iv	22.4[a]	22.9[a]	1.034	0.7

Table 11. Breast cancer with bone metastases: median time to skeletal-related event *(Continued)*

Bone-targeted agents vs bisphosphonate						
Fizazi 2009 (N = 44)	Denosumab 180 mg sc every 4 weeks	Bisphosphonate iv (clinician choice)	NR	NR	NR	NR
Lipton 2008 (N = 255)	Denosumab sc every 4 weeks (30 mg, 120 mg or 180 mg) or every 12 weeks (60 mg or 180 mg)	Bisphosphonate iv (either zoledronate, pamidronate or ibandronate)	NR	NR	NR	NR
Stopeck 2010 (N = 2046)	Denosumab 120 mg sc (iv placebo)	Zoledronate 4 mg iv (sc placebo)	Not yet reached	26.4	0.82	0.01
Standard vs reduced bisphosphonate/bone agent						
CALGB-70604 2015 (N = 820)	Zoledronate 4 mg iv every 4 weeks	Zoledronate 4 mg iv every 12 weeks	NR	NR	NR	NR
Fizazi 2009 (N = 73)	Denosumab 180 mg sc every 4 weeks	Denosumab 180 mg sc every 12 weeks	NR	NR	NR	NR
OPTIMIZE-2 2014 (N = 403)	Zoledronate 4 mg iv every 4 weeks	Zoledronate 4 mg iv every 12 weeks	NR "Median time to first SRE was not estimable because there were too few events to calculate the median" (clinical trials registry record)	NR	NR	NR
ZOOM 2013 (N = 425)	Zoledronate 4 mg iv every 4 weeks	Zoledronate 4 mg iv every 12 weeks	NR "Median time to first on-study skeletal-related event could not be calculated because of the very low event rate."	NR	NR	NR

iv: intravenous; **N**: total number of women in each study; **NR**: not reported; **NS**: not significant; **sc**: subcutaneous; **SMPR**: skeletal morbidity period rate; **SRE**: skeletal-related event.

[a]We converted data from weeks or days into months.

[b]Trial authors did not provided numerical value for median TSE of control and treatment groups.

Table 12. Breast cancer with bone metastases: median survival time

Study	Bisphosphonate	Comparator	Median survival (months)		Ratio: bisphosphonate/comparator	P value reported
			Bisphosphonate	Comparator		
Bisphosphonate vs placebo/open						
AREDIA 1998 (N = 751)	Pamidronate 90 mg iv	Placebo	19.8	17.8	1.11	0.98
Body 2003 (N = 312)	Ibandronate 6 mg iv	Placebo	28.3[a]	26.7[a]	1.06	NS
Body 2004 (N = 564)	Ibandronate 50 mg oral	Placebo	NR	NR	NR	NS
Conte 1996 (N = 295)	Pamidronate 45 mg iv	Open	19.4	21	0.92	NS
Elomaa 1983 (N = 34)	Clodronate 1600 mg oral	Placebo	25	14	1.78	0.004
Heras 2009 (N = 150)	Ibandronate 6 mg iv	Placebo	NR	NR	NR	NR
Hultborn 1999 (N = 404)	Pamidronate 60 mg iv	Placebo	18.3	18.3	1.00	NS
Kohno 2005 (N = 228)	Zoledronate 4 mg iv	Placebo	NR	NR	NR	NR
Kristensen 1999 (N = 100)	Clodronate 800 mg oral, 2/d for 2 years	Open	18.3	18	1.02	0.97
Martoni 1991 (N = 38)	Clodronate 300 mg oral	Placebo	NR	NR	NR	NR
Paterson 1993 (N = 173)	Clodronate 800 mg oral, 2/d for up to 3 years	Placebo	NR	NR	NR	0.198
Tripathy 2004 (N = 287)	Ibandronate 50 mg oral	Placebo	NR	NR	NR	NR
Tubiana-Hulin 2001 (N = 144)	Clodronate 1600 mg oral	Placebo	NR	NR	NR	NR
Van-Holten 1987 (N = 161)	Pamidronate 150 mg oral, 2/d indefinitely	Open	25	24	1.04	NS
Direct comparisons of different bisphosphonate regimens						
Diel 1999 (N = 318)	Pamidronate 60 mg iv	Clodronate 2400 mg oral or 900 mg iv	NR	NR	NR	NR

Table 12. Breast cancer with bone metastases: median survival time *(Continued)*

Rosen 2004 (N = 1130)	Zoledronate 4 mg iv	Pamidronate 90 mg iv	NR	NR	NR	NR
von Au 2016 (N = 375)	Pamidronate 60 mg iv	Clodronate 900 mg iv every 3 weeks or 2400 mg/d oral	NR	NR	NR	NR
ZICE 2014 (N = 1404)	Ibandronate 50 mg oral	Zoledronate 4 mg iv	26.1	25.6	1.02 Hazard ratio = 1.086 (95% confidence interval 0.948 to 1.245)	0.24
Bone-targeted agents vs bisphosphonate						
Fizazi 2009 (N = 44)	Denosumab 180 mg sc every 4 weeks	Bisphosphonate iv (clinician choice)	NR	NR	NR	NR
Lipton 2008 (N = 255)	Denosumab sc every 4 weeks (30 mg, 120 mg or 180 mg) or every 12 weeks (60 mg or 180 mg)	Bisphosphonate iv (either zoledronate, pamidronate or ibandronate)	NR	NR	NR	NR
Stopeck 2010 (N = 2046)	Denosumab 120 mg sc (iv placebo)	Zoledronate 4 mg iv (sc placebo)	NR	NR	0.95 Actual median overall survival values are not reported, but about 60% of participants alive at 27 months in both arms according to Kaplan-Meier curve	0.49
Standard vs reduced bisphosphonate/bone agent						
CALGB-70604 2015 (N = 820)	Zoledronate 4 mg iv every 4 weeks	Zoledronate 4 mg iv every 12 weeks	NR	NR	NR	NR
Fizazi 2009 (N = 73)	Denosumab 180 mg sc every 4 weeks	Denosumab 180 mg sc every 12 weeks	NR	NR	NR	NR

Table 12. Breast cancer with bone metastases: median survival time *(Continued)*

OPTIMIZE-2 2014 (N = 403)	Zoledronate 4 mg iv every 4 weeks	Zoledronate 4 mg iv every 12 weeks	NR	NR	NR	NR
ZOOM 2013 (N = 425)	Zoledronate 4 mg iv every 4 weeks	Zoledronate 4 mg iv every 12 weeks	NR	NR	NR	NR

iv: intravenous; **N**: total number of women in each study; **NR**: not reported; **NS**: not significant; **sc**: subcutaneous
[a]We converted data from weeks into months.

Table 13. Breast cancer with bone metastases: bone pain

Study	Bisphosphonate	Comparator	Bone pain		Pain tool used	P value reported
			Bisphosphonate	Comparator		
Bisphosphonate vs placebo/open						
AREDIA 1998 (N = 751)	Pamidronate 90 mg iv	Placebo	A significant difference in mean change from baseline pain score favouring pamidronate was first noted at 24 months		Reference to validation	P = 0.015
Body 2003 (N = 312)	Ibandronate 6 mg iv	Placebo	Significantly improved bone pain score over time favouring the ibandronate 6 mg group compared to placebo		5-point scale. No reference to validation	P < 0.001
Body 2004 (N = 564)	Ibandronate 50 mg oral	Placebo	At week 96, mean bone pain scores were significantly reduced from baseline with ibandronate compared to placebo (-0.10, 95% CI -0.32 to 0.02 vs 0.20, 95% CI 0.07 to 0.34)		Participant-rated scale	P = 0.001
Conte 1996 (N = 268)	Pamidronate 45 mg iv	Open	No significant difference between the groups at the predefined time points; most symptomatic variables showed a greater degree of improvement in the pamidronate group		6-point self-assessment scale	NS
Elomaa 1983 (N = 34)	Clodronate 1600 mg oral	Placebo	NR	NR	NR	NR
Heras 2009 (N = 150)	Ibandronate 6 mg iv	Placebo	NR	NR	NR	NR
Hultborn 1999 (N = 404)	Pamidronate 60 mg iv	Placebo	"...results favoured pamidronate however insignificant when corrected for the prestudy values" (page 3387)		Questionnaire & VAS	NS
Kohno 2005 (N = 268)	Zoledronate 4 mg iv	Placebo	From weeks 4-52, a chart of mean change in the BPI was statistically significant in favour of a reduction by zoledronic acid		BPI	NR
Kristensen 1999 (N = 100)	Clodronate 800 mg oral, 2/d for 2 years	Open	No difference between groups using a physician-rated scale (no reference to validation)		Physician-rated scale. No	NS

Table 13. Breast cancer with bone metastases: bone pain *(Continued)*

					reference to validation	
Martoni 1991 (N = 38)	Clodronate 300 mg oral	Placebo	No significant difference		Scott-Huskinsson Visual Analog method	NS
Paterson 1993 (N = 173)	Clodronate 800 mg oral, 2/d for up to 3 years	Placebo	NR	NR	NR	NR
Tripathy 2004 (N = 287)	Ibandronate 50 mg oral	Placebo	From baseline to study end point, bone pain scores increased by +0.21 in the placebo group and a slight increase of +0.03 in the ibandronate 50 mg group		4-point scale	P = 0.201
Tubiana-Hulin 2001 (N = 144)	Clodronate 1600 mg oral	Placebo	Significant reduction in pain in clodronate group compared to control group		Visual pain scale. No reference to validation	P = 0.01
Van-Holten 1987 (N = 161)	Pamidronate 150 mg oral, 2/d indefinitely	Open	Bone scores were significantly higher in the control group with an early reduction in bone pain within the first 3 months of pamidronate. However, bone pain then increased significantly over time (P = 0.005) in both groups although more rapidly in the control than pamidronate group (P = 0.02)		3 items on bone pain within a quality-of-life questionnaire designed specifically for this trial. Reliability of the questionnaire tested at first observation point of participants	P = 0.007 (pamidronate vs control at 3 months)
Direct comparisons of different bisphosphonate regimens						
Diel 1999 (N = 318)	Pamidronate 60 mg iv	Clodronate 2400 mg oral or 900 mg iv	Trend to improvement with iv bisphosphonates (30% reduction with pamidronate iv, 25% reduction with clodronate iv) compared with oral clodronate (15%)		Pain tool not reported in abstract	NR
Rosen 2004 (N = 766)	Zoledronate 4 mg iv	Pamidronate 90 mg iv	No difference		BPI	NS
von Au 2016 (N = 375)	Pamidronate 60 mg iv	Clodronate 900 mg iv every 3 weeks or 2400 mg/d oral	Pain scores at baseline and final examinations were not significantly different among the groups. Overall, a slight increase in pain scores over time with no significant differences among the groups (P = 0.36)		VAS	NS

Table 13. Breast cancer with bone metastases: bone pain *(Continued)*

ZICE 2014 (N = 1404)	Ibandronate 50 mg oral	Zoledronate 4 mg iv	Pain scores reduced from baseline at 12 weeks and were maintained over 96 weeks. There was no difference between the groups		BPI	NS
Bone-targeted agents vs bisphosphonate						
Fizazi 2009 (N = 44)	Denosumab 180 mg sc every 4 weeks	Bisphosphonate iv (clinician choice)	NR	NR	NR	NR
Lipton 2008 (N = 255)	Denosumab sc every 4 weeks (30 mg, 120 mg or 180 mg) or every 12 weeks (60 mg or 180 mg)	Bisphosphonate iv (either zoledronate, pamidronate or ibandronate)	NR	NR	NR	NR
Stopeck 2010 (N = 2046)	Denosumab 120 mg sc (iv placebo)	Zoledronate 4 mg iv (sc placebo)	Prolonged median time to develop moderate/severe pain from no pain on baseline (denosumab: zoledronate hazard ratio 0.78). Lower proportion of participants with moderate/severe pain from no pain on baseline (denosumab 14.8% vs zoledronate 26.7% at week 73)		BPI	P < 0.05
Standard vs reduced bisphosphonate/bone agent						
CALGB-70604 2015 (N = 820)	Zoledronate 4 mg iv every 4 weeks	Zoledronate 4 mg iv every 12 weeks	NR	NR	NR	NR
Fizazi 2009 (N = 73)	Denosumab 180 mg sc every 4 weeks	Denosumab 180 mg sc every 12 weeks	NR	NR	NR	NR
OPTIMIZE-2 2014 (N = 189)	Zoledronate 4 mg iv every 4 weeks	Zoledronate 4 mg iv every 12 weeks	Change from baseline in mean BPI score was 0.24 (standard deviation 1.976) in zoledronate every 4 weeks while the change from baseline score was 0.31 (standard deviation 2.099) in zoledronate every 12 weeks		BPI	NR
ZOOM 2013 (N = 425)	Zoledronate 4 mg iv every 4 weeks	Zoledronate 4 mg iv every 12 weeks	Most people had a score < 4; median pain at rest and pain on movement scores were < 4 at all points in both groups		Validated 6-point Verbal Rating Scale	NS

BPI: Brief Pain Inventory; **CI**: confidence interval; **iv**: intravenous; **N**: total number of women in each study; **NR**: not reported; **NS**: not significantly different; **sc**: subcutaneous; **VAS**: visual analogue scale

Table 14. Breast cancer with bone metastases: quality of life

Study	Questionnaires used	Summary of findings
Bisphosphonate vs placebo/open		

Table 14. Breast cancer with bone metastases: quality of life *(Continued)*

AREDIA 1998	Spitzer Quality-of-Life Index scores	"...quality of life scores worsened from baseline to the last visit in both groups, although less so in the pamidronate group (P = 0.057 and 0.088, respectively)" (page 1087)
Body 2003	EORTC Quality of Life Scale - Core 30 questionnaire (QLQ-C30)	"...overall quality of life scores decreased to a lesser extent between baseline and last assessment for patients receiving 2 mg ibandronate (-18.1) and 6 mg ibandronate (-10.3) compared with patients receiving placebo (-45.4)" (page 1709)
Body 2004	EORTC QLQ-C30	Global quality of life scores decreased significantly during the study, though significantly less with ibandronate than with placebo (-8.3, 95% CI -20.6 to 4.1 vs -26.8, 95% CI -39.4 to 14.3, P = 0.03)
Conte 1996	NR	NR
Elomaa 1983	NR	NR
Heras 2009	NR	NR
Hultborn 1999	NR	NR
Kohno 2005	NR	NR
Kristensen 1999	EORTC QLQ-C30	"There was no significant difference between patients receiving clodronate and controls in the change from baseline to 3 or 6 months in any of the 17 quality-of-life variables" (page 71)
Martoni 1991	NR	NR
Paterson 1993	NR	NR
Tripathy 2004	NR	NR
Tubiana-Hulin 2001	NR	NR
Van-Holten 1987	A questionnaire was developed specifically for the trial (validated 4-point ordinal scale). The 4 items were related to mobility impairment, gastrointestinal toxicity, bone pain and fatigue	The mean mobility impairment score was higher in the control group than the pamidronate group (P = 0.03). Similarly, bone pain scores were higher in the control group compared to pamidronate (P = 0.007). No differences were noted in fatigue or gastrointestinal toxicity between the two groups
Direct comparisons of different bisphosphonate regimens		
Diel 1999	NR	NR
Rosen 2004	FACT-G	No significant difference between groups. Quality-of-life data reported in conference presentation only
von Au 2016	NR	NR
ZICE 2014	EORTC QLQ-C30	No difference
Bone-targeted agents vs bisphosphonate		

Table 14. Breast cancer with bone metastases: quality of life *(Continued)*

Fizazi 2009	NR	NR
Lipton 2008	NR	NR
Stopeck 2010	FACT-G	"...over monthly time points during an 18-month period, an average of 10% more patients in the denosumab group compared with the zoledronic acid group had a clinically meaningful improvement in HRQoL (> 5-point increase in FACT-G total score) over the course of the study. An average of 7% fewer patients in the denosumab group than in the zoledronic acid group had worsening of HRQoL on study" (page 7, Clinical Cancer Research)
Standard vs reduced bisphosphonate/bone agent		
CALGB-70604 2015	NR	NR
Fizazi 2009	NR	NR
OPTIMIZE-2 2014	NR	NR
ZOOM 2013	NR	NR

CI: confidence interval; **EORTC**: European Organisation for the Research and Treatment of Cancer; **NR**: not reported

Table 15. Breast cancer with bone metastases: toxicity - osteonecrosis of the jaw, hypocalcaemia, renal dysfunction & drug-related death

Study	Treatment vs comparator	Osteonecrosis of the jaw		Hypocalcaemia		Renal dysfunction		Drug-related death	
		Bone agent (n/N)	Comparator (n/N)	Bone agent (n/N)	Comparator (n/N)	Bone agent (n/N)	Comparator (n/N)	Bone agent (n/N)	Comparator (n/N)
Bisphosphonate vs placebo/open									
AREDIA 1998	Pamidronate 90 mg iv vs placebo	NR	NR	One participant had a "symptomatic hypocalcemia episode" (page 1088): 1/367	0/384	NR	NR	0/182	0/189
Body 2003	Ibandronate 6 mg iv vs placebo	NR	NR	NR	NR	No difference between ibandronate and control		0/154	0/158
Body 2004	Ibandronate 50 mg oral vs placebo	NR	NR	27/286	14/277	15/286 "renal AEs". "No reports of serious AEs (renal failure) in the active treatment group" (page 1136)	13/277 "renal AEs"	0/286	0/277
Conte 1996	Pamidronate 45 mg iv vs open	NR	NR	Transient asymptomatic hypocalcemia: 24/143	Transient asymptomatic hypocalcaemia: 9/152	NR	NR	NR	NR
Elomaa 1983	Clodronate 1600 mg oral vs placebo	NR	NR	NR	NR	NR	NR	NR	NR

Table 15. Breast cancer with bone metastases: toxicity - osteonecrosis of the jaw, hypocalcaemia, renal dysfunction & drug-related death *(Continued)*

Heras 2009	Ibandronate 6 mg iv vs placebo	0/75	0/75	NR	NR	No comparable differences between ibandronate and control		NR	NR
Hultborn 1999	Pamidronate 60 mg iv vs placebo	NR	NR	NR	NR	NR	NR	NR	NR
Kohno 2005	Zoledronate 4 mg iv vs placebo	NR	NR	G1: 44/114, G2&3: 0/114; G4: 1/114	G1: 8/113; G2&3: 0/113; G4: 1/113	0/114	0/113	NR	NR
Kristensen 1999	Clodronate 800 mg oral, 2/d for 2 years vs open	NR	NR	13/49	2/51	NR	NR	NR	NR
Martoni 1991	Clodronate 300 mg oral vs placebo	NR	NR	0/19	0/19	0/19	0/19	NR	NR
Paterson 1993	Clodronate 800 mg oral bid for up to 3 years vs placebo	NR	NR	NR	NR	NR	NR	NR	NR
Tripathy 2004	Ibandronate 50 mg oral vs placebo	NR	NR	10/148	6/143	10/148	6/143	0/148	0/143
Tubiana-Hulin 2001	Clodronate 1600 mg oral vs placebo	NR	NR	NR	NR	NR	NR	NR	NR
Van-Holten 1987	Pamidronate 150 mg oral, 2/d indefinitely vs open	NR	NR	NR	NR	1/81 "gradual deterioration in kidney function during 40 months of study"	0/80	NR	NR
Direct comparisons of different bisphosphonate regimens									
Diel 1999	Pamidronate 60 mg iv vs Clodronate 2400 mg oral or 900 mg iv	NR	NR	NR	NR	NR	NR	NR	NR

Table 15. Breast cancer with bone metastases: toxicity - osteonecrosis of the jaw, hypocalcaemia, renal dysfunction & drug-related death *(Continued)*

Rosen 2004	Zoledronate 4 mg iv vs Pamidronate 90 mg iv	NR	NR	NR	NR	Renal toxicity was greater in the zoledronate arm and was dependent on the dose and infusion time, compared to the pamidronate arm		NR	NR
von Au 2016	Pamidronate 60 mg iv vs Clodronate 900 mg iv every 3 weeks or 2400 mg/d oral	NR	NR	NR	NR	NR	NR	NR	NR
ZICE 2014	Ibandronate 50 mg oral vs Zoledronate 4 mg iv	5/704	9/697	G3/4: 4/704	G3/4: 4/697	172/704 "renal toxic effects"	226/697 "renal toxic effects"	3/704	4/697
Bone-targeted agents vs bisphosphonate									
Fizazi 2009	Denosumab 180 mg sc every 4 weeks or every 12 weeks vs Bisphosphonate iv (clinician choice)	NR	NR	G3/4: 7/73	G/3/4: 1/35	NR	NR	0/73	0/35
Lipton 2008	Denosumab sc every 4 weeks (30 mg, 120 mg or 180 mg) or every 12 weeks (60 mg or 180 mg) vs Bisphosphonate iv (either zoledronate, pamidronate or ibandronate)	0/211	0/43	NR	NR	No significant renal impairment in either arm		0/211	0/43
Stopeck 2010	Denosumab 120 mg sc (iv placebo) vs Zoledronate 4 mg iv (sc placebo)	26/1020	18/1013	62/1020	37/1013	50/1020. Renal failure: 2/1020	86/1013. Renal failure: 25/1013	NR	NR
Standard vs reduced bisphosphonate/bone agent									
CAL-GB-70604 2015	Zoledronate 4 mg iv every 4 weeks vs	NR (reported for breast,	NR	NR	NR	NR	NR	NR	NR

Table 15. Breast cancer with bone metastases: toxicity - osteonecrosis of the jaw, hypocalcaemia, renal dysfunction & drug-related death *(Continued)*

	Zoledronate 4 mg iv every 12 weeks	prostate and multiple myeloma patients)							
Fizazi 2009	Denosumab 180 mg sc every 4 weeks vs Denosumab 180 mg sc every 12 weeks	NR	NR	NR	NR	"denosumab did not affect renal function" (page 1569). Data were not reported separately for denosumab every 4 weeks and every 12 weeks		0/38	0/35
OPTIMIZE-2 2014	Zoledronate 4 mg iv every 4 weeks vs Zoledronate 4 mg iv every 12 weeks	2[a]/198	2[a]/202	1[a]/198	2[a]/202	Renal failure: 0[a]/198	Renal failure: 2[a]/202	NR	NR
ZOOM 2013	Zoledronate 4 mg iv every 4 weeks vs Zoledronate 4 mg iv every 12 weeks	4/209	3/216	NR	NR	1/209 "renal adverse event"	2/216 "renal adverse event"	0/209	0/216

AE: adverse event; **G**: grade; **iv**: intravenous; **n**: number of events; **N**: number of women studies in each group; **NR**: not reported; **sc**: subcutaneous
[a]Reported as serious adverse events.

Table 16. Breast cancer with bone metastases: toxicity - nausea, gastrointestinal events, fatigue & fever

Study	Treatment vs comparator	Nausea		GI events		Fatigue		Fever	
		Bone agent (n/N)	Comparator (n/N)	Bone agent (n/N)	Comparator (n/N)	Bone agent (n/N)	Comparator (n/N)	Bone agent (n/N)	Comparator (n/N)
Bisphosphonate vs placebo/open									
AREDIA 1998	Pamidronate 90 mg iv vs placebo	NR	NR	NR	NR	147/367	112/386	51/367	19/386
Body 2003	Ibandronate 6 mg iv vs placebo	NR	NR	NR	NR	NR	NR	NR	NR
Body 2004	Ibandronate 50 mg oral vs placebo	10/286	4/277	6/286	2/277	NR	NR	NR	NR

Table 16. Breast cancer with bone metastases: toxicity - nausea, gastrointestinal events, fatigue & fever *(Continued)*

Conte 1996	Pamidronate 45 mg iv vs open	NR	NR	NR	NR	NR	NR	7/143	5/152
Elomaa 1983	Clodronate 1600 mg oral vs placebo	NR	NR	NR	NR	NR	NR	NR	NR
Heras 2009	Ibandronate 6 mg iv vs placebo	NR	NR	NR	NR	NR	NR	NR	NR
Hultborn 1999	Pamidronate 60 mg iv vs placebo	NR	NR	NR	NR	NR	NR	NR	NR
Kohno 2005	Zoledronate 4 mg iv vs placebo	57/114	60/113	19/114	8/113	51/114	36/113	63/114	37/113
Kristensen 1999	Clodronate 800 mg oral, 2/d for 2 years vs open	NR	NR	NR	NR	NR	NR	NR	NR
Martoni 1991	Clodronate 300 mg oral vs placebo	NR	NR	NR	NR	NR	NR	NR	NR
Paterson 1993	Clodronate 800 mg oral, 2/d for up to 3 years vs placebo	NR	NR	Non-specific GI symptoms: 2/85	Non-specific GI symptoms: 1/88	NR	NR	NR	NR
Tripathy 2004	Ibandronate 50 mg oral vs placebo	7/148	3/143	Upper GIT events: 10% and similar to placebo		NR	NR	NR	NR
Tubiana-Hulin 2001	Clodronate 1600 mg oral vs placebo	7/69	9/68	4/49	4/68	1/69	0/68	NR	NR
Van-Holten 1987	Pamidronate 150 mg oral, 2/d indefinitely vs open	NR	NR	18/81	0/80	NR	NR	NR	NR
Direct comparisons of different bisphosphonate regimens									
Diel 1999	Pamidronate 60 mg iv vs Clodronate 2400 mg oral or 900 mg iv	NR	NR	14/112	NR	NR	NR	NR	NR
Rosen 2004	Zoledronate 4 mg iv vs Pamidronate 90 mg iv	355/742	179/388	NR	NR	294/742	159/388	231/742	103/388

Table 16. Breast cancer with bone metastases: toxicity - nausea, gastrointestinal events, fatigue & fever *(Continued)*

von Au 2016	Pamidronate 60 mg iv vs Clodronate 900 mg iv every 3 weeks or 2400 mg/d oral	NR	NR	14/109	900 mg iv every 3 weeks: 11/105; 2400 mg oral daily: 24/107	NR	NR	NR	NR
ZICE 2014	Ibandronate 50 mg oral vs Zoledronate 4 mg iv	G3/4: 41/704	G3/4:38/697	G3/4: 8/704 "dyspepsia"	G3/4: 2/697 "dyspepsia"	G3/4: 98/704	G3/4: 97/697	G3/4:12/704	G3/4: 18/697
Bone-targeted agents vs bisphosphonate									
Fizazi 2009	Denosumab 180 mg sc every 4 weeks or every 12 weeks vs Bisphosphonate iv (clinician choice)	17/73	7/35	NR	NR	8/73	4/35	NR	NR
Lipton 2008	Denosumab sc every 4 weeks (30 mg, 120 mg or 180 mg) or every 12 weeks (60 mg or 180 mg) vs Bisphosphonate iv (either zoledronate, pamidronate or ibandronate)	36/211	8/43	NR	NR	28/211	5/43	13/211	10/43
Stopeck 2010	Denosumab 120 mg sc (iv placebo) vs Zoledronate 4 mg iv (sc placebo)	356/1020	384/1013	NR	NR	301/1020	324/1013	170/1020	247/1013
Standard vs reduced bisphosphonate/bone agent									
CAL-GB-70604 2015	Zoledronate 4 mg iv every 4 weeks vs Zoledronate 4 mg iv every 12 weeks	NR	NR	NR	NR	NR	NR	NR	NR
Fizazi 2009	Denosumab 180 mg sc every 4 weeks	NR	NR	NR	NR	NR	NR	NR	NR

Table 16. Breast cancer with bone metastases: toxicity - nausea, gastrointestinal events, fatigue & fever *(Continued)*

	vs Denosumab 180 mg sc every 12 weeks								
OPTIMIZE-2 2014	Zoledronate 4 mg iv every 4 weeks vs Zoledronate 4 mg iv every 12 weeks	2/198	2/202	2/198 "abdominal pain"	5/202 "abdominal pain"	1/198	2/202	1/198	0/202
ZOOM 2013	Zoledronate 4 mg iv every 4 weeks vs Zoledronate 4 mg iv every 12 weeks	G3/4: 24/209	G3/4: 33/216	65/209	91/216	G3/4:18/209	G3/4: 19/216	G3/4: 22/209	G3/4: 28/216

G: grade; **iv**: intravenous; **n**: number of events; **N**: number of women studies in each group; **NR**: not reported; **sc**: subcutaneous

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Breast Neoplasms] explode all trees
#2 breast near cancer*
#3 breast near neoplasm*
#4 breast near carcinoma*
#5 breast near tumour*
#6 breast near tumor*
#7 #1 or #2 or #3 or #4 or #5 or #6
#8 MeSH descriptor: [Diphosphonates] explode all trees
#9 biphosphonate*
#10 bisphosphanate*
#11 diphosphonate*
#12 diphosphanate*
#13 MeSH descriptor: [Etidronic Acid] explode all trees
#14 etidronate*
#15 MeSH descriptor: [Clodronic Acid] explode all trees
#16 clodronate*
#17 pamidronate*
#18 MeSH descriptor: [Alendronate] explode all trees
#19 alendronate*
#20 risedronate*
#21 tiludronate*
#22 ibandronate*
#23 zoledronate*
#24 incadronate*
#25 olpadronate*
#26 neridronate*
#27 MeSH descriptor: [RANK Ligand] explode all trees
#28 RANK ligand inhibitor
#29 denosumab
#30 prolia
#31 Xgeva
#32 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31
#33 #7 and #32

Appendix 2. MEDLINE (via OvidSP) search strategy

1	randomised controlled trial.pt.
2	randomized controlled trial.pt.
3	controlled clinical trial.pt.
4	randomized.ab.
5	randomised.ab.
6	placebo.ab.
7	randomly.ab.
8	trial.ab.
9	groups.ab.

(Continued)

10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11	exp Breast Neoplasms/
12	(breast adj6 cancer$).mp.
13	(breast adj6 neoplasm$).mp.
14	(breast adj6 carcinoma$).mp.
15	(breast adj6 tumo?r$).mp.
16	or/11-15
17	exp Diphosphonates/
18	biphosphonate$.mp.
19	bisphosphanate$.mp.
20	diphosphonate$.mp.
21	diphosphanate$.mp.
22	exp Etidronic Acid/
23	etidronate$.mp.
24	exp Clodronic Acid/
25	clodronate$.mp.
26	pamidronate$.mp.
27	exp Alendronate/
28	alendronate.mp.
29	risedronate$.mp.
30	tiludronate$.mp.
31	ibandronate$.mp.
32	zoledronate$.mp.
33	incadronate$.mp.
34	olpadronate$.mp.
35	neridronate$.mp.
36	RANK Ligand/
37	RANK ligand.mp.

(Continued)

38	RANK ligand inhibitor$.mp.
39	denosumab.mp.
40	prolia.mp.
41	Xgeva.mp.
42	or/17-41
43	and/10,16,42
44	limit 43 to (humans and yr="2010 -Current")

Appendix 3. Embase (via OvidSP) search strategy

1	Randomized controlled trial/
2	Controlled clinical study/
3	Random$.ti,ab.
4	randomization/
5	intermethod comparison/
6	placebo.ti,ab.
7	(compare or compared or comparison).ti.
8	(open adj label).ti,ab.
9	((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.
10	double blind procedure/
11	parallel group$1.ti,ab.
12	(crossover or cross over).ti,ab.
13	((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.
14	(assigned or allocated).ti,ab.
15	(controlled adj7 (study or design or trial)).ti,ab.
16	(volunteer or volunteers).ti,ab.
17	trial.ti.
18	or/1-17

(Continued)

19	exp breast/
20	exp breast disease/
21	(19 or 20) and exp neoplasm/
22	exp breast tumor/
23	exp breast cancer/
24	exp breast carcinoma/
25	(breast$ adj5 (neoplas$ or cancer$ or carcin$ or tumo$ or metasta$ or malig$)).ti,ab.
26	19 or 20 or 21 or 22 or 23 or 24 or 25
27	exp bisphosphonic acid derivative/
28	biphosphonate$.mp.
29	bisphosphanate$.mp.
30	diphosphonate$.mp.
31	diphosphanate$.mp.
32	exp etidronic acid/
33	etidronate$.mp.
34	exp clodronic acid/
35	clodronate$.mp.
36	exp pamidronic acid/
37	pamidronate$.mp.
38	exp alendronic acid/
39	alendronate$.mp.
40	exp risedronic acid/
41	risedronate$.mp.
42	exp tiludronic acid/
43	tiludronate$.mp.
44	exp ibandronic acid/
45	ibandronate$.mp.
46	exp zoledronic acid/

(Continued)

47	zoledronate$.mp.
48	exp incadronic acid/
49	incadronate$.mp.
50	exp olpadronic acid/
51	olpadronate$.mp.
52	exp neridronic acid/
53	neridronate$.mp.
54	rank ligand.mp.
55	(rank and ligand).mp.
56	exp denosumab/
57	denosumab$.mp.
58	prolia$.mp.
59	xgeva$.mp.
60	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59
61	18 and 26 and 60
62	limit 61 to (human and embase)

Appendix 4. WHO ICTRP search strategy

Basic Search:

1. breast cancer AND bisphosphonate*
2. breast cancer AND biphosphonate
3. breast cancer AND biphosphonates
4. breast cancer AND biphosph*
5. breast cancer AND diphosphonate*
6. breast cancer AND diphosphonate
7. breast cancer AND diphosphonates
8. breast cancer AND diphosph*
9. breast cancer AND denosumab
10. breast cancer AND RANK ligand

Advanced Search:

1. Condition: breast cancer
Intervention: bisphosphon% OR diphosphon% OR zoledron%
Recruitment Status: ALL

2. Condition: breast cancer
Intervention: clodron% OR etidron% OR alendron%
Recruitment Status: ALL

3. Condition: breast cancer
Intervention: ibandron%
Recruitment Status: ALL

4. Condition: breast cancer
Intervention: pamidron%
Recruitment Status: ALL

5. Condition: breast cancer
Intervention: risedron%
Recruitment Status: ALL

6. Condition: breast cancer
Intervention: tiludron% OR incadron% OR olpadron% OR neridron%
Recruitment Status: ALL

7. Condition: breast cancer
Intervention: RANK ligand
Recruitment Status: ALL

8. Condition: breast cancer
Intervention: denosumab OR prolia or xgeva
Recruitment Status: ALL

Appendix 5. ClinicalTrials.gov search strategy

Basic Search

1. Breast cancer AND Bisphosphonates
2. Breast cancer AND Diphosphonates
3. Breast cancer AND Denosumab
4. Breast cancer AND “RANK ligand”

Advanced Search

1. Condition: Breast cancer OR "Breast Neoplasms"
Interventions: Bisphosphonates OR Diphosphonates OR Zoledronate OR "Zoledronic acid" OR clodronate OR "Clodronic acid" OR "Etidronic acid" OR Alendronate OR Ibandronate OR Pamidronate OR Risedronate OR Tiludronate OR Incadronate OR Olpadronate OR Neridronate
Recruitment: All studies
Study results: All studies
Study type: Interventional Study
Gender: All studies

2. Condition: Breast cancer OR "Breast Neoplasms"
Interventions: Denosumab OR Prolia OR Xgeva OR "RANK ligand"
Recruitment: All studies
Study results: All studies
Study type: Interventional Study
Gender: All studies

FEEDBACK

Elomaa 1983, 2 December 2008

Summary

A reader has suggested that Elomma reference should be 1993 and not 1983.

Reply

The reference for the Elomaa trial is correct.

WHAT'S NEW

Date	Event	Description
7 November 2018	Review declared as stable	This broad topic will be split into two topics. One topic will assess the role of bone-modifying agents in early breast cancer, and the second topic will assess the role of these agents in metastatic breast cancer

HISTORY

Protocol first published: Issue 4, 2000
Review first published: Issue 1, 2002

Date	Event	Description
19 September 2016	New search has been performed	Performed searches for new studies on 19 September 2016
19 September 2016	New citation required but conclusions have not changed	Included 10 new studies with outcome data, 5 already identified studies with new data or updated data, and 18 ongoing studies. This led to 20,212 new participants being added to this updated review
30 April 2011	New citation required but conclusions have not changed	13 new studies included, adding denosumab. Amended title to include "other bone agents"
30 April 2011	New search has been performed	Performed searches for new studies on 30 April 2011
14 May 2008	Amended	Converted to new review format
22 August 2006	Amended	Minor update
24 May 2005	New search has been performed	Update of review - new search conducted
29 November 2001	New search has been performed	First review publication

CONTRIBUTIONS OF AUTHORS

Original review: Dr Nick Pavlakis, Robert Schmidt and Dr Martin Stockler were the primary authors.
2012 update: Dr Matthew Wong and Dr Nick Pavlakis were the primary authors, with Dr Martin Stockler resolving disagreement and critiquing the review update methodology and results.
2016 update: Dr Brent O'Carrigan, Melina Willson and Dr Annabel Goodwin were the main authors with Dr Annabel Goodwin leading the review, and Dr Matthew Wong, Dr Martin Stockler, and Dr Nick Pavlakis reviewing the draft review.

DECLARATIONS OF INTEREST

BOC: none known
MW: none known
MLW: none known
MS: none known
NP: none known
AG: none known

SOURCES OF SUPPORT

Internal sources

- NHMRC Clinical Trials Centre, The University of Sydney, Australia.

External sources

- National Institute for Health Research/Department of Health Cochrane Review Incentive Scheme 2010, UK.
- Cochrane Review Support Programme 2016, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. The 'Types of Interventions' section has been revised to explicitly state that other bone-acting agents (including denosumab) can be included in the review. Although this was already stated underneath the main list, we have brought this information upfront.
2. Cochrane's 'Risk of bias' tool has been fully integrated to comply with Cochrane standards. Performance and detection bias has been split into one domain on 'blinding of participants and personnel' and a second domain on 'blinding of outcome assessment'
3. We have integrated the GRADE approach in the 2016 review update and developed a 'Summary of findings' table for each setting. The MERGE criteria used in previous versions of this review has been removed. Previous MERGE assessments can be found in former versions of this published review in the Cochrane Library
4. A number of new outcomes have been listed under the 'Types of outcome measures' section however most of these outcomes (e.g. skeletal-related event rate and bone pain for breast cancer with bone metastases, and bone metastases for early breast cancer) were part of the previous version of the review but were not fully listed in each section of the review. In addition, we added disease-free survival to the early breast cancer section for this review update. We also grouped the main toxicities for each treatment setting in separate tables and provided frequencies if reported in the trial publications.
5. We conducted analyses of overall survival and disease-free survival data using time-to-event data in the early breast cancer studies, in addition to the analyses using dichotomous data. This was because analyses using time-to-event data are generally considered more appropriate than dichotomous data for outcomes such as overall survival and disease-free survival.
6. Some minor transcriptional errors were noted in previous versions of the review and these have been corrected in the 2016 review update.

NOTES

The authors of the 2011 review update made modifications to the search strategies. They added the search terms "Denosumab" (including Prolia and Xgeva) and "RANK ligand" to the MEDLINE, Embase and WHO ICTRP search strategies, simplified the search strategy for WHO ICTRP to include all breast cancer stages, and broadened the search for bisphosphonates. The search strategy for ClinicalTrials.gov and CENTRAL was also included in this review update.

We updated this review in April 2011, with 13 new studies and 6 updates. The meta-analysis is now formally divided into three settings: BCBM, ABC without bone metastases and EBC. The search strategy is included as a flow diagram in Figure 1. We used both MERGE criteria and Risk of Bias Tables to assess the quality of studies.

In terms of future updates of this review, this broad topic will be split into two topics. One topic will assess the role of bone-modifying agents in early breast cancer, and the second topic will assess the role of these agents in metastatic breast cancer.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Bone Density Conservation Agents [*therapeutic use]; Bone Neoplasms [mortality] [*prevention & control] [*secondary]; Breast Neoplasms [mortality] [*pathology]; Clodronic Acid [therapeutic use]; Denosumab [therapeutic use]; Diphosphonates [*therapeutic use]; Imidazoles [therapeutic use]; Injections, Intravenous; Randomized Controlled Trials as Topic; Zoledronic Acid

MeSH check words

Female; Humans